



REVIEW

World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia, Part 2: Long-term treatment of schizophrenia

PETER FALKAI¹, THOMAS WOBROCK¹, JEFFREY LIEBERMAN², BIRTE GLENTHOJ³,
WAGNER F. GATTAZ⁴, HANS-JÜRGEN MÖLLER⁵ & WFSBP Task Force on Treatment
Guidelines for Schizophrenia*

¹Department of Psychiatry and Psychotherapy, University of Saarland, Homburg/Saar, Germany, ²Department of Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, ³Department of Psychiatry, University of Copenhagen, Bispebjerg Hospital, Denmark, ⁴Department of Psychiatry, University of Sao Paulo, Brazil, and ⁵Department of Psychiatry and Psychotherapy, University of Munich, Munich, Germany

Abstract

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

Key words: Schizophrenia, long-term treatment, evidence-based medicine, practice guidelines, biological treatment, anti-psychotics

EXECUTIVE SUMMARY OF RECOMMENDATIONS

General recommendations

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 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 on the

* Jeffrey Lieberman (Chairman; USA), Birte Glenthoj (Co-Chairman; Denmark), Wagner F. Gattaz (Co-Chairman; Brazil), Peter Falkai (Secretary; Germany), Thomas Wobrock (Co-Secretary; Germany), Hans-Jürgen Möller (Chairman of the WFSBP Scientific Publication and Guideline Task Force Committee; Germany), A. Carlo Altamura (Italy), Nancy Andreasen (USA), Thomas R.E. Barnes (UK), Helmut Beckmann (Germany), Jorge Ciprian-Ollivier (Argentina), Tim Crow (UK), Anthony David (UK), Michael Davidson (Israel), Bill Deakin (UK), Helio Elkis (Brazil), Lars Farde (Sweden), Wolfgang Gaebel (Germany), Bernd Gallhofer (Germany), Jes Gerlach (Denmark), Steven Richard Hirsch (UK), Carlos R. Hojaj (Australia), Assen Jablensky (Australia), John Kane (USA), Takuja Kojima (Japan), Lars von Knorring (Sweden), Patrick McGorry (Australia), Herbert Meltzer (USA), Driss Moussaoui (Morocco), Franz Müller-Spahn (Switzerland), Jean-Pierre Olie (France), A. Pacheco Palha (Portugal), Mitsumoto Sato (Japan), Heinrich Sauer (Germany), Nina Schooler (USA), Daniel Weinberger (USA), Shigeto Yamawaki (Japan).

Correspondence: Thomas Wobrock, MD, Department of Psychiatry and Psychotherapy, University of Saarland, Kirrberger Strasse, D-66421 Homburg/Saar, Germany. Tel: +49 6841 16 24216. Fax: +49 6841 16 24270. E-mail: thomas.wobrock@uniklinik-saarland.de

background of adequately provided information and his personal goals in order to find common ground to encourage a 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 reduction in symptoms, 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 the level of functioning and quality of life, to prevent relapse, and to ensure that monitoring for adverse treatment effects continues. 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 demonstrated effectiveness during the stable phase. The selection of appropriate psychosocial treatments is 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 well-being and quality of life.

Specific treatment recommendations

Long-term treatment is indicated for all patients with schizophrenia. If the patient has improved with a particular medication regimen, continuation of that regimen and monitoring are recommended for at least 6 months in the stabilisation phase. Premature lowering of dose may lead to a recurrence of symptoms and relapse. 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 a duration of 1–2 years in first-episode patients, 2–5 years in patients with one relapse and over 5 years (maybe even throughout life) in multiepisode patients. Antipsychotic monotherapy should be preferred. Continuous dosing strategies have shown superiority compared to intermittent-dose strategies. 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 evidence that high maintenance doses (e.g., for first-generation antipsychotics (FGAs) above 600 mg CPZ equivalents) are more effective in prevent-

ing relapse than standard doses. First-episode patients may require lower doses in relapse prevention than multiepisode patients. Second-generation antipsychotics (SGAs) have proven similar or superior efficacy of preventing relapse and suppression (or even improvement) of symptoms compared to FGAs (evidence for periods of up to 2 years is available from studies of the specific agents). Atypical or typical depot preparations should be preferred 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. Antipsychotic medications are associated with differing risks of a variety of side effects, including neurological, metabolic, sexual, endocrine, sedative and cardiovascular side effects. These side effects may have an even greater influence on the choice of medication in the long-term than in the acute phase 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 weight gain, extrapyramidal symptoms (EPS) (especially tardive dyskinesia), and 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. 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. SGAs have clear advantages with respect to EPS (especially tardive dyskinesia) and may have advantages in improving cognitive deficits, negative and depressive symptoms, subjective well-being and quality of life compared to FGAs. These advantages have to be weighed against other side effects, e.g., a higher risk of weight gain and diabetes mellitus with some agents. 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. In primary negative symptoms treatment options include switching to an atypical antipsychotic or augmentation strategies. 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 also address prominent mood lability and benzodiazepines are helpful for managing anxiety and insomnia. Further treatment strategies, including appropriate management of side effects, are

extensively discussed in the respective section of the guideline below.

General aspects of the WFSBP guidelines on long-term treatment of schizophrenia

Introduction

Schizophrenia is a major psychotic disorder (or cluster of disorders) that presents an enormous burden to the patients and their relatives. Schizophrenic patients suffer considerable distress, a decreased quality of life, either for a variable length of time or continuously, and long-term disabilities which can have negative effects on employment, financial income, relationships and life satisfaction. After the resolution of the acute phase the disorder may persist and periods of remission alternate with periods of exacerbation. Sometimes a number of negative symptoms not unlike the symptoms in the prodromal phase may be seen. The efficacy and effectiveness of antipsychotic treatment not only in the acute phase, but also in the stabilisation and maintenance phase of schizophrenia has been proven by standard research and well established by clinical trials (DGPPN 1998; NICE 2002; APA 2004). To reduce the burden of the disease it is of great importance to develop successful treatment strategies, including multidimensional approaches. Pharmacologic antipsychotic treatment should always be accompanied by psychotherapeutic intervention and complemented with psychosocial strategies.

This second part of the guideline and the presented recommendations focus on the long-term treatment of schizophrenia. The guideline is aimed to help clinicians, service users and care givers become aware of the different treatments available and be useful in assessing the respective evidence.

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. They therefore provide an update of the contemporary knowledge about various aspects of schizophrenia, especially treatment options. The aim of these guidelines is to improve standards of care, diminish unacceptable variations in the provision and quality of care, and support physicians in clinical decision-making. Although these guidelines favour particular treatments on the basis of the available evidence, the treating physician remains responsible for his assessment and treatment choice. These guidelines are primarily concerned with the biological (somatic)

treatment of adults and address recommendations in this field. The specific aim of these guidelines is to evaluate the role of pharmacological agents in the treatment and management of schizophrenia, while the role of specific psychological interventions and specific service delivery systems is covered only briefly. The effectiveness of somatic treatment is considered.

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

Methods of literature research and data extraction

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

American Psychiatric Association, Practice Guideline for the Treatment of Patients with Schizophrenia (APA 1997), and American Psychiatric Association, Practice Guideline for the Treatment of Patients with Schizophrenia, Second Edition (APA 2004);

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

National Institute for Clinical Excellence, Core Interventions in the Treatment of Schizophrenia London (NICE 2003), and National Institute for Clinical Excellence, Guidance on the Use of Newer (Atypical) Antipsychotic Drugs for the Treatment of Schizophrenia (NICE 2002);

Royal Australian and New Zealand College of Psychiatrists, Australian and New Zealand Clinical Practice Guideline for the Treatment of Schizophrenia, draft only (RANZCP 2003), and Summary Australian and New Zealand Clinical Practice Guideline for the Treatment of Schizophrenia (McGorry et al. 2003);

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

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

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

The Mount Sinai Conference on the Pharmacotherapy of Schizophrenia (Marder et al. 2002);

The Texas Medication Algorithm Project (TMAP) Schizophrenia Algorithms (Miller et al. 1999);

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

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

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

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

Evidence-based classifications of recommendations

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

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

Level B. There is fair research-based evidence to support this recommendation. The evidence was obtained from at least two moderately large, positive, randomised, double-blind trials (this can be either two or more comparator studies or one comparator-controlled and one placebo-controlled study) or

from one moderately large, positive, randomised, double-blind study (comparator-controlled or placebo-controlled) and at least one prospective moderately large (sample size equal to or greater than 50 participants), open-label, naturalistic study.

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

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

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

General aspects of long-term treatment of schizophrenia

Indication and goals of long-term treatment for schizophrenia

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, support of developing 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 to continue that regimen for at least 6 months (APA 2004). It is also critical to assess continuing side effects that may have been present in the acute phase and to adjust pharmacotherapy accordingly to minimise adverse side effects that may otherwise lead to medication nonadherence and relapse.

The *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 the level of functioning and quality of life, that increases in symptoms or relapses are effectively treated, and that monitoring for adverse treatment effects continues. For most persons with schizophrenia in the stable phase, psychosocial interventions are recommended as a useful adjunctive treatment to pharmacological treatment to improve outcome. The main aims of pharmacological intervention in the stable phase are to prevent relapse, help keep a person 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 he agrees, with family members, relatives, care givers and, in some cases, advocates, in the sense of providing adequate information and with an understanding of the patient's personal goals. When 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 well-being 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 schizophrenic patients medication self-management (e.g., benefits of maintenance antipsy-

chotic 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).

Antipsychotic treatment

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 phase 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). Antipsychotics are also necessary for psychological treatments to be effective. On the other hand, psychosocial interventions are always an essential element in addition to pharmacotherapy (McGorry et al. 2003). Targets of long-term treatment include maintenance therapy to stabilise remission and 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 in his or her treatment programme (APA 2004). However, the frequency of assessments by the psychiatrist or member of the team depends on the specific nature of the treatment and expected fluctuations of the illness. For example, patients given depot antipsychotic medications must be evaluated at least monthly, patients receiving clozapine must be evaluated weekly in the first 18 weeks and then monthly, and those who are going through potentially stressful changes in their lives should sometimes be assessed daily (APA 1997).

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. Antipsychotic drugs, atypical or conventional, should not be prescribed concurrently, except 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) (APA 1997, 2004; DGPPN 1998; Working Group for the Canadian Psychiatric Association 1998; NICE 2002; McGorry et al. 2003).

It is important to define target symptoms of long-term treatment and 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. In primary negative symptoms treatment options include switching to an atypical antipsychotic or augmentation strategies (for detailed information see Part 1 of these guidelines, Falkai et al. 2005). 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 also address prominent mood lability and benzodiazepines are helpful for managing anxiety and insomnia (see Part 1 of these guidelines, Falkai et al. 2005).

In Tables I and II dosages of commonly used antipsychotics are recommended for long-term treatment.

Comparative efficacy of antipsychotics. As mentioned for the acute treatment of schizophrenia (see Part 1 of these guidelines, Falkai et al. 2005), there is still an ongoing controversial debate whether or not SGAs as a group are superior to FGAs in their efficacy and effectiveness in the long-term treatment of schizophrenia. Recent meta-analyses reported the crucial points in the published randomised, controlled studies (Sartorius et al. 2002). In a systematic overview and meta-regression analysis of short- and long-term randomised controlled trials, substantial heterogeneity was observed in the study results comparing SGAs to FGAs, which was partially accounted for by the dose of the FGAs used. When the dose was about 12 mg/day of haloperidol

(or equivalent), atypical antipsychotics were found to have no benefits in terms of efficacy or overall tolerability, but to cause fewer extrapyramidal side effects (Geddes et al. 2000). In a meta-analysis of randomised efficacy trials comparing SGAs and FGAs, and comparing between different SGAs, effect sizes of clozapine, amisulpride, risperidone and olanzapine were greater than those of FGAs, and the effect size of zotepine was marginally greater, while other SGAs revealed no clear superiority (Davis et al. 2003). No efficacy difference was detected among amisulpride, risperidone and olanzapine when directly compared to each other. No evidence was found that the haloperidol dose (or all FGA comparators converted to haloperidol-equivalent doses) affected these results. In a review of studies evaluating efficacy and tolerability of olanzapine, risperidone, quetiapine and sertindole, superiority to placebo was reported (Leucht et al. 1999). Quetiapine and sertindole were found to be comparable to haloperidol, while olanzapine and risperidone showed slightly superior efficacy in the treatment of global schizophrenic symptoms. In addition, olanzapine and risperidone were found to demonstrate slight superiority in improvement of negative symptoms. All SGAs were noted to be associated with less frequent EPS measured as the use of antiparkinsonian medications compared to haloperidol. A meta-analysis of all randomised controlled trials in which SGAs had been compared with low-potency (equivalent or less potent than chlorpromazine) FGAs found that as a group, SGAs were moderately

Table I. Recommended dosages of oral antipsychotic medications in long-term treatment.

Antipsychotic	DI ¹	First-episode patients (mg/day)	Multi-episode patients (mg/day)	Maximal dose ² (acute) (mg/day)
<i>SGA</i>				
Amisulpride	(1)–2	200	400–800	1200
Aripiprazole	1	15	15–30	30
Clozapine	2–(4)	100–500	200–600	900
Olanzapine	1	5–20	10–20	20*
Quetiapine	2	300–600	400–750	750*
Risperidone	1–2	2–4	3–6	16
Ziprasidone	2	80–160	120–160	160*
Zotepine	2–(4)	50–150	100–200	450*
<i>FGA</i>				
Chlorpromazine	2–4	200–500	300–600	1000
Fluphenazine	2–3	2.5–12.5	5–15	20–(40)
Flupentixol	1–3	2–10	3–15	60
Haloperidol	(1)–2	1–5	5–10	100
Perazine	1–2	50–200	100–300	1000
Perphenazine	1–3	6–36	12–42	56
Pimozide	1–2	2–6	2–8	16
Zuclopenthixol	1–3	2–5	2–25	75

¹DI (dose intervals): recommended distribution of the daily dose: once = 1; twice = 2; etc.

²Dosages above the mentioned range are not approved in many countries, but in clinical practice and clinical studies some SGAs (*) are even dosed higher.

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

Antipsychotic	DI (dose intervals, weeks)	First-episode patients (mg)	Multiepisode patients (mg)
<i>SGA</i>			
Risperidone microspheres	2	25	25–50
<i>FGA</i>			
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

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

In this context it is noteworthy that it has never been claimed that SGAs are generally more efficacious than FGAs, but that in terms of global efficacy they are equally efficacious in positive symptoms and that they have some advantages in reducing negative, depressive and cognitive symptoms. The major advantage of the SGAs is their generally better EPS tolerability (Correll et al. 2004). The clinical profile of equal efficacy in positive symptoms and low risk of extrapyramidal side effects are the main ingredients of the term ‘atypical neuroleptic’, realised in the best sense by the first atypical antipsychotic, clozapine (Möller 2000, 2004a). Insofar the discussion about the advantages of SGAs should not focus too much on efficacy but more on the advantages in terms of reduced extrapyramidal side effects, as well as on the broader spectrum of efficacy. It should also be noted that meta-analyses are only one approach of evidence-based medicine, and that also the traditional qualitative systematic review of studies is important (Maier and Möller 2005).

Keeping this conflicting points of view in mind, the available RCTs of SGAs versus FGAs in long-term treatment are presented and discussed in these guidelines.

Duration of long-term treatment. Schizophrenia is a chronic, recurrent disease. One of the main targets of long-term antipsychotic treatment is thus the prevention of relapse. The definitions of relapse vary between studies. For example, relapse has been defined as hospitalisation for psychopathology (Tran et al. 1998); an increase of positive symptoms (three or more BPRS items) which did not respond to a dose increase (Speller et al. 1997); and multiple criteria like hospitalisation, increased level

of care and 20% PANSS increase, self-injury, suicide or homicidal ideation or violent behaviour, or CGI > 6 (Csernansky et al. 2002). The vast majority of patients who do not undergo any form of antipsychotic therapy experience a relapse within 3–5 years. As a consequence of this finding continuous neuroleptic treatment was recommended over a period of several years (Kissling 1991). When the effects of discontinuing antipsychotic drugs, either after an acute psychotic episode or during long-term treatment, are examined, the subsequent rate of relapse seems to be similar. Individuals who are well stabilised on maintenance medication show high rates of relapse when their antipsychotic is discontinued or switched to placebo (NICE 2002). Around 20% of individuals will only experience a single episode (Möller 2004), while a similar percentage will experience a relapse despite continued antipsychotic drug treatment. Nevertheless, 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 people with very brief psychotic episodes without negative psychosocial consequences, and the uncommon patient for whom all available antipsychotics pose a significant health risk (NICE 2002). It is clear from the placebo-controlled RCTs and discontinuation studies that the efficacy of antipsychotics in relapse prevention is established (DGPPN 1998; NICE 2002; APA 2004) (*Level A*). Effective long-term treatment may be limited by frequent patient preference for discontinuation of medication and by the number of side effects reported.

Treatment strategies. The traditional method of long-term drug treatment of schizophrenia is the continuation of neuroleptic treatment for one or more years. 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 continuation treatment as they result in a higher frequency of relapse and hospital admissions (Schooler 1993; Schooler et al. 1997; Gaebel et al. 2002) (*Level A*).

Special aspects of long-term treatment of schizophrenia

Relapse prevention in first episode patients

Approximately 20% of those patients who experience a first psychotic episode do not subsequently experience any new psychotic symptoms. To date, however, there are no clearly prognostic predictors or factors which allow any estimation of response to pharmacological therapy and long-term course. In a 5-year follow-up study, only 13.7% of patients with a first episode met full recovery criteria for 2 years or longer (Robinson et al. 2004). Remission was predicted by a shorter period of psychosis prior to study entry, and better cognitive functioning. Although there has been very little study of factors that act to maintain recovery in remitted first-episode patients, evidence suggests that antipsychotics are highly effective in prevention of relapse (APA 2004). In patients for whom antipsychotics are prescribed, 1-year relapse risk varies from 0 to 46%, with relapse rates of patients who discontinue taking medication being up to five times higher than for those who continue treatment (e.g., Kane et al. 1982; Crow et al. 1986; McCreddie et al. 1989; Robinson et al. 1999b) (*Level A*). The varying relapse rates found in these studies may be due to differences in the criteria used to define relapse, different study populations and different lengths of follow-up, and could in part be explained by different adherence to maintenance medication. Relapses are even common during the first 5 years after a first episode of psychosis, a phase that has been termed the 'critical period' (McGorry et al. 2003). In one study, 82% of first-episode patients relapsed within 5 years (Robinson et al. 1999b). It is essential that high quality and intensive biopsychosocial care is provided continuously and assertively during this critical period. In addition to maintenance antipsychotic medication, other potential strategies to maintain recovery in remitted first-episode patients include enhancing stress management and eliminating exposure to cannabinoids and psychostimulants (APA 2004). Psychiatrists may experience pressure from patients and their families to discontinue antipsychotic medication after patients recover from a first episode of schizophrenia, but follow-up studies indicate that the rate of relapse

after a first episode is relatively high. About 40–60% of untreated patients relapse within a year after recovery. Therefore continuation of medication may play an important role in relapse prevention.

Efficacy of first-generation antipsychotics. There are only a few randomised controlled studies available that compare FGA to placebo in maintenance treatment and relapse prevention in the special population of first-episode schizophrenia. A systematic review identified six randomised controlled studies evaluating maintenance treatment in these patients showing efficacy in relapse prevention (Bradford et al. 2003) (*Level A*). Maintenance treatment with fluphenazinedecanoate revealed significantly superior efficacy in relapse prevention compared to placebo (relapse rate in 1 year 0% with fluphenazine versus 41% with placebo) (Kane et al. 1982). In another study there were significantly fewer relapsed patients treated with flupenthixol decanoate (at least 40 mg/month i.m.), chlorpromazine (at least 200 mg/day), haloperidol (at least 3 mg/day), pimozide (at least 4 mg/day) or trifluoperazine (at least 5 mg/day) compared to placebo over a period of 6–24 months (46 versus 62%) (Crow et al. 1986).

Efficacy of second-generation antipsychotics. In an ongoing randomised, double-blind, multi-centre study, risperidone is being compared to low-dose haloperidol in the first treatment year, and continued neuroleptic treatment to prodrome-based early intervention (intermittent treatment) in the second year. Preliminary results demonstrate that treatment in first-episode schizophrenia is effective under both neuroleptics; however, these patients are at high risk for treatment drop-out (Gaebel et al. 2004). Based on the results and extension phases of acute treatment studies in first-episode patients, and on subsets of patients of maintenance studies with SGAs, it was concluded that SGAs also have similar or superior efficacy compared to FGAs in the long-term management of first-episode schizophrenia.

In a randomised double-blind study comparing risperidone and haloperidol, psychopathology scores and disease severity improved significantly, with no significant differences between groups (Schooler et al. 2005). The median time to relapse was significantly greater in the risperidone group. There were significantly more extrapyramidal signs and symptoms and adjunctive medication use in the haloperidol group, and greater prolactin elevation in the risperidone group. However, RCTs for this population comparing other SGAs to placebo or to

FGAs are still lacking and the evidence for efficacy of SGAs in terms of relapse prevention in first-episode patients is limited (*Level B*). Currently, some RCTs comparing SGAs with FGAs in the maintenance treatment of first-episode patients are underway (e.g., EUFEST).

Dosage. If a patient has improved with a particular medication regimen, continuation of that regimen and monitoring are recommended for at least 6 months (stabilisation phase) and at least 1 year with lowered dose, if possible (DGPPN 1998; APA 2004). Premature lowering of dose may lead to a recurrence of symptoms and relapse. Most guidelines recommend lower dosages for first-episode schizophrenia than for multiepisode or chronic patients, although the empirical basis for this recommendation is sparse. This strategy may result from increased side effects observed in first-episode patients, especially a higher vulnerability to EPS (see section on acute phase treatment). Therefore in maintenance therapy dosages at the lower end of the dose range are recommended.

Duration of treatment. At least 1–2 years of maintenance treatment with antipsychotic medication is recommended for remitted patients after a first episode (e.g., DGPPN 1998; NICE 2002; APA 2004). Although this may be longer than current practice in many settings, it is recommended because the social deterioration and potential losses following a relapse may be severe. Although this recommendation was made by a consensus of experts in the field, the empirical basis for this strategy is currently sparse and will remain so until more well-designed double-blind randomised studies in first-episode schizophrenia are conducted (Gaebel et al. 2004). However, recent data suggest that even in patients who initially respond well to treatment, relapse risk is unacceptably high (Schooler et al. 2005). There are considerations that the severity of the first episode and the level of remission may be additional parameters determining the recommended duration of treatment in first-episode schizophrenia. Patients with full remission may be tapered off after 12 months (Gaebel et al. 2002), and patients who have experienced a more severe episode or were slow to respond should be maintained for 24 months or even longer (*Level D*). Based on the argument of the high relapse rate, a longer duration of relapse prevention by continuing antipsychotic medication regimen is being discussed (Robinson et al. 2004; Schooler et al. 2005).

Relapse prevention in multiepisode patients

In multiepisode patients strategies of relapse prevention, dosage and duration of treatment may differ from those in first-episode patients. After a number of relapses the probability of achieving full remission may be reduced.

Efficacy of first-generation antipsychotics. The efficacy of typical antipsychotic medications in relapse prevention has been demonstrated in numerous studies. Approximately 70% of patients who receive no active antipsychotic therapy experience a further relapse in the following year, whereas the relapse rate in patients treated with conventional neuroleptic agents is approximately 30% (Davis 1975). After 2 years, approximately 80% of non-treated and 50% of treated patients relapse once more (APA 1997; NICE 2002). In a meta-analysis of 35 RCTs, relapse was reported in 55% of those who were randomised to receive placebo, but in only 21% of those receiving conventional antipsychotics (Davis et al. 1993) (*Level A*). Reviewing antipsychotic withdrawal studies, the mean cumulative relapse rate in the withdrawal groups was 53% (follow up of 6–10 months) compared with 16% (follow up of 8 months) during maintenance therapy (Gilbert et al. 1995) (*Level A*). Over a period of several years, continuing treatment with conventional antipsychotics can reduce the risk of relapse by up to two thirds (Kissling 1991).

Efficacy of second-generation antipsychotics. A meta-analysis including six double-blind RCTs comparing SGAs with placebo clearly demonstrated efficacy for SGAs in relapse prevention (Leucht et al. 2003b) (*Level A*). Overall, in relapse prevention atypical antipsychotic medications are markedly superior as a group compared with placebo, whereby this superiority has been demonstrated in individual studies for olanzapine, ziprasidone and zotepine, but not for amisulpride (NICE 2002).

Compared with typical antipsychotic medications, a meta-analysis of 11 double-blind RCTs revealed slight but significant superiority of atypical antipsychotic medications as a group in terms of their efficacy in relapse prevention compared to FGAs (Leucht et al. 2003b) (*Level A*). The annual additional risk reduction for relapse was 8% (35% reduction of the relative risk for relapse), if atypical rather than typical antipsychotic medications were used. It remained unclear whether the advantages of atypical antipsychotic medications in relapse prevention were due to better efficacy, better tolerability or better compliance. For pooled data from the single studies, only risperidone (Csernansky et al. 2002;

Marder et al. 2003) and olanzapine (Tran et al. 1998), but not clozapine (Essock et al. 1996a,b; Rosenheck et al. 1999a,b, 2000; Tamminga et al. 1994) or amisulpride (Speller et al. 1997), were shown to be significantly superior to FGA (Leucht et al. 2003b). Although the relapse rate was not significantly reduced, clozapine treatment was associated with a longer stay in the community setting (Leucht et al. 2003b) and lower readmission rates (Essock et al. 1996a,b). In a naturalistic study the time to readmission for patients discharged with atypical (risperidone, olanzapine) and typical neuroleptics was measured over two years (Rabinowitz et al. 2001) (*Level C*). The readmission rate favoured the second-generation antipsychotics. There were significantly fewer relapses under risperidone and olanzapine compared with haloperidol, but not in comparison to other atypical antipsychotic medications (Leucht et al. 2003b). In a 3-year naturalistic study, risperidone and olanzapine demonstrated lower relapse rates than haloperidol and quetiapine (Dossenbach et al. 2005) (*Level C*).

Dosage. A number of studies investigated treatment regimens where lower dosages of FGAs were used in maintenance therapy than during acute treatment. The results showed that, compared with continuous therapy, relapse rates increased slightly within acceptable limits (e.g., Hogarty et al. 1988; Dixon et al. 1995) (*Level A*). The lower dosages were, however, associated with a more favourable side effect profile and better compliance. A further strategy is low-dose, continuous depot medication and additional administration of oral medication upon the occurrence of early prodromal signs. This method appears to be suitable for making low-dose therapies more effective and safer (Marder et al. 1994) (*Level D*).

Duration of treatment. After the first relapse, maintenance therapy should last at least 2–5 years (NICE 2002; APA 2004) (*Level D*). This recommendation is based on clinical experience, withdrawal studies and follow-up studies showing that 5 years after an acute episode may be a critical period for relapse. However, there are no studies longer than 5 years in the literature and clinical experience with individual patients treated by the same clinician is also sparse. 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.

Early intervention. 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 dysphoric symptoms, such as tension and nervousness, eating less, difficulty concentrating and remembering, trouble 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 symptoms, changes in observable behaviours are noted by some patients and families. Examples include social withdrawal, wearing make-up in excessive or bizarre ways, and loss of concern about one's appearance (APA 1997). Controlled studies have demonstrated that specific programmes to educate patients and families about prodromal symptoms and early intervention when symptoms occur can be helpful in reducing relapse rates (APA 1997, 2004) (*Level B*). One part of early intervention may also be to reinstall pharmacological treatment if withdrawn, or to increase the dose of the current antipsychotic. Despite neuroleptics the use of benzodiazepines may be helpful to reduce the anxiety and tension often associated with a beginning relapse (Carpenter et al. 1999; APA 2004) (*Level C*).

Improvement of symptoms

Beside relapse prevention, goals of long-term treatment are to ensure that symptom control is sustained, that the patient is maintaining or improving the level of functioning and quality of life, that increases in symptoms or relapses are effectively treated, and that monitoring for adverse treatment effects continues. As a consequence of these aims of long-term treatment, many studies have not only evaluated the efficacy of antipsychotics in terms of relapse prevention, but also in terms of symptomatic improvement.

Efficacy of first-generation antipsychotics. Meta-analyses of double-blind RCTs revealed superior efficacy for symptom improvement and global clinical outcome for haloperidol (Joy et al. 2004) and chlorpromazine (Thornley et al. 2004) compared to placebo. Several guidelines refer to these results (e.g., APA 1997).

Efficacy of second-generation antipsychotics. Amisulpride (400–1000 mg/day) demonstrated comparable efficacy in improvement of positive symptoms and

global psychopathology compared to risperidone (4–10 mg/day) over 6 months, and demonstrated better overall response (Sechter et al. 2002). Similar results, including superior improvement in negative symptoms, were observed in a 12-month, double-blind RCT of amisulpride (200–800 mg/day) versus haloperidol (5–20 mg/day) (Colonna et al. 2000). In an RCT in patients with predominantly negative symptomatology, amisulpride at low doses was also superior in improving negative symptoms (Speller et al. 1997). Therefore amisulpride was concluded to be more effective in the control of psychotic symptoms and improving quality of life and social functioning than haloperidol (Lecrubier et al. 2002). In addition another RCT revealed similar improvement with amisulpride compared to olanzapine (Mortimer et al. 2004). In summary, there is convincing evidence for the efficacy of amisulpride in improving symptoms in chronic schizophrenia (*Level A*).

In RCTs of 6–12 months duration, *aripiprazole* (15–30 mg/day) revealed superiority in symptom improvement compared to placebo (Pigott et al. 2003), and comparable efficacy compared to haloperidol (Kasper et al. 2003) and olanzapine (Kujawa et al. 2004) in positive symptoms; at doses of 30 mg/day it showed slightly superior improvement in negative symptomatology compared to haloperidol (Kasper et al. 2003). In summary, there is good evidence for the efficacy of aripiprazole for the treatment of chronic schizophrenia (*Level A*).

Clozapine revealed superiority in improving positive symptoms during a long-term RCT (over 6 months) compared to haloperidol (Kane et al. 2001), an effect that could be confirmed in further open trials (Essock et al. 1996a,b; Rosenheck et al. 1999a,b). Clozapine showed its ability to improve significantly negative symptoms compared to FGAs in an open, 1-year study (Meltzer et al. 1989). In summary, there is fair research-based evidence for the efficacy of clozapine in improving symptoms of chronic schizophrenic patients over a long time (*Level B*).

Quetiapine showed improvement of symptoms and continued efficacy in open trials in long-term treatment, including negative symptomatology (Buckley 2004; Cheer and Wagstaff 2004; Kasper et al. 2004), and comparable efficacy, e.g., to risperidone (Mullen et al. 2001). However, double-blind RCTs are lacking to date. There is only very limited evidence for efficacy of quetiapine in the long-term treatment of schizophrenia (*Level C*).

Superiority in improving positive symptoms was observed for *olanzapine* (5–20 mg/day) compared to haloperidol (5–20 mg/day) (Tollefson et al. 1997). Furthermore, two extension phase studies showed

superior improvement in negative symptoms, quality of life and social functioning (Revicki et al. 1999; Hamilton et al. 2000). Comparable efficacy in positive symptoms and superiority in improvement of negative symptoms was found in comparison to risperidone (mean dose 7 mg/day) (Tran et al. 1997), but this finding with respect to negative symptomatology could not be confirmed in a later 12-week study using a lower risperidone dosage (Conley and Mahmoud 2001). Compared to fluphenazine, olanzapine showed superior improvement in positive symptoms and global psychopathology (Dossenbach et al. 2004). To summarise, there is convincing evidence for the efficacy of olanzapine in long-term treatment (*Level A*).

Additionally *risperidone* demonstrated either superiority with a flexible dosage option (Csernansky et al. 2002) or comparable efficacy (Marder et al. 2003) compared to haloperidol in two 2-year, double-blind RCTs. In a non-comparative open trial in first-episode patients, low-dose risperidone (lower than 6 mg/day) was concluded to be effective and well tolerated, and significant improvements could be maintained over 1 year of treatment (Huq et al. 2004). In summary there is good evidence for the efficacy of risperidone in long-term treatment (*Level A*).

In a 28-week RCT, *ziprasidone* (80–160 mg/day) showed a similar outcome with respect to positive symptoms and superiority in improving negative symptoms compared to haloperidol (5–15 mg/day) (Hirsch et al. 2002). A double-blind RCT comparing ziprasidone with placebo showed significant advantages for ziprasidone in patients with predominant negative symptomatology after a 1-year treatment (Arato et al. 2002). In summary, there is fair research-based evidence for the efficacy of ziprasidone in the long-term treatment of chronic schizophrenic patients (*Level B*).

Zotepine revealed superior improvement in positive but not negative symptoms compared to placebo in a 26-week RCT (Cooper et al. 2000). Compared to haloperidol zotepine showed greater reduction in negative symptomatology (Barnas et al. 1992). In summary, there is limited evidence for the efficacy of zotepine in long-term treatment of chronic schizophrenic patients (*Level B*).

In an 18-month RCT comparing the relative effectiveness of a first-generation antipsychotic, perphenazine, with different newer antipsychotics (CATIE study), the time to the discontinuation of treatment for any cause (mostly inefficacy or side effects) was significantly longer in the olanzapine (7.5–30 mg/day) group than in the quetiapine (200–800 mg/day) or risperidone (1.5–6 mg/day) group, but not in the perphenazine (8–32 mg/day) or

ziprasidone (40–160 mg/day) group. It was concluded that olanzapine was most effective in terms of the rates of discontinuation, and the efficacy of the conventional antipsychotic agent perphenazine appeared similar to that of quetiapine, risperidone, and ziprasidone (Lieberman et al. 2005). The conclusions of the study seem questionable due to the fact that the results may be biased as patients with tardive dyskinesia were excluded from the perphenazine group after randomisation. For this reason the advantages of the SGAs over the FGA (perphenazine) may have been underestimated.

Long-acting depot medication

Poor and partial adherence to antipsychotic treatment is a major problem in the long-term management of schizophrenia. A direct relationship between partial medication adherence and hospitalisation risk could be demonstrated (Weiden et al. 2004). The development of long-acting depot antipsychotics therefore provided an important option, especially in the management of partial nonadherence.

Long-acting depot antipsychotics mostly consist of an ester of the neuroleptic 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. This allows relatively stable plasma drug levels to be achieved over long periods, allowing the injections to be given every 2–4 weeks. Disadvantages of the depot formulation are a diminished flexibility of administration, with adjustment to the optimal dosage being a protracted and uncertain process, and the risks of pain, oedema, pruritis and sometimes a palpable mass at the injection site. Nevertheless, some people receiving depot antipsychotics prefer them to oral antipsychotics, largely because they consider them to be more convenient (Walburn et al. 2001) (*Level A*).

While in placebo-controlled studies there is only proven efficacy of fluphenazine decanoate and risperidone microspheres in relapse prevention (Adams et al. 2001; Kane et al. 2003), the evidence for other depot formulations is assumed because their oral forms displayed sufficient effectiveness in preventing relapse in long-term treatment, e.g., haloperidol (Joy et al. 2004). A systematic review concluded that in mirror-image studies the number of hospitalisations decreased after initiation of depot medication in schizophrenic patients who had previously been taking solely oral antipsychotics (Davis et al. 1994) (*Level C*). In a meta-analysis there was no clear evidence that depot antipsychotics differ significantly from oral conventional antipsychotics in terms of relapse rates, numbers of participants leaving the study early or side effects (David and Adams 2001)

(*Level A*). The meta-analysis includes studies of as short a duration as 6 weeks, which may not reflect real aspects of long-term treatment with a long-acting medication. Long-acting depot antipsychotics do not appear to be associated with an increased risk of movement disorders compared to oral conventional antipsychotics. Further results of this meta-review referring to 92 RCTs involving five depot preparations (flupentixol decanoate, fluphenazine decanoate, haloperidol decanoate, pipotiazine palmitate and zuclopenthixol decanoate) were that there is some limited evidence to suggest that depot medications, as compared to oral conventional antipsychotics, may confer some advantages in terms of global functioning. There was no convincing evidence for the superiority of any one type of depot, although some limited evidence suggests that zuclopenthixol decanoate may be associated with a lower risk of relapse than either flupentixol decanoate or haloperidol decanoate. In addition, the use of fluphenazine decanoate may be associated with a greater risk of movement disorders (as indicated by the use of anticholinergic drugs) relative to the other depots. The use of low-dose depot preparations was found to be less effective than standard doses, but high-dose depot medications did not appear to be more effective.

A pharmacokinetic approach could be particularly valuable because there is a high interindividual variability in plasma levels using standard dosages of long-acting preparations, as in the case of haloperidol decanoate (Altamura et al. 2003). When switching from oral to parenteral administration of the same antipsychotic (e.g., haloperidol), comparable plasma levels may not be reached. This can account for early relapse or poor response to a long-acting antipsychotic treatment (Altamura et al. 1990). In addition plasma levels may be useful to predict and explain unwanted side effects of depot antipsychotics (Altamura et al. 1985).

Long-acting risperidone is the first and, at the time of development of this guideline, the only available atypical antipsychotic in depot formulation. The preparation consists of an aqueous suspension of microspheres comprising risperidone and a biodegradable copolymer, and the injection interval is 2 weeks. With this new mechanism, significant release of risperidone starts 3 weeks after the first injection, and is followed by gradual and sustained release for 4–6 weeks after the first injection (Harrison and Goa 2004). There is evidence for superior efficacy compared to placebo (Kane et al. 2003b) (*Level C*), no significant difference compared to oral risperidone in short- to medium-term RCTs (Harrison and Goa 2004) (*Level C*), and limited evidence for long-term effec-

tiveness in a 1-year open label trial comparing two different doses (25 vs. 50 mg) of long-acting risperidone (Fleischhacker et al. 2003). However, long-term studies comparing long-acting risperidone to oral antipsychotics are still needed.

Summarised recommendations for long-term treatment

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 (e.g., NICE 2002; APA 2004). If possible and required, family members, caregivers and in some cases advocates should also be included in the decision process. In long-term treatment, the antipsychotic medication which was able to achieve remission with the most favourable side effect profile should be given. 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 evidence that high maintenance doses (e.g., more than 600 mg CPZ equivalents for FGAs) are more effective in preventing relapse than standard doses. First-episode patients may require lower doses in relapse prevention than multipisode 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. Second-generation antipsychotics have proven similar or superior efficacy in preventing relapse and suppression (or even improvement) of symptoms compared to FGAs (available studies of the specific agents supply evidence for periods of up to 2 years). Due to the decreased risk of EPS, especially tardive dyskinesia, and, as observed in most studies, the superior efficacy in improving negative, cognitive and depressive symptoms together with at least comparable (for some agents, e.g., risperidone, olanzapine, superior) efficacy in relapse prevention, second-generation antipsychotics should be preferred in long-term treatment (e.g., NICE 2002). It is not recommended to change from a typical to an atypical neuroleptic agent if there is currently good symptom control and no occurrence of severe side effects (DGPPN 1998; NICE 2002; APA 2004), although the probable decreased risk of tardive dyskinesia when switching to an atypical agent should be discussed with the patient. As continuous dosing strategies revealed superiority compared to intermittent-dose strategies,

continuous oral 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 through the exchange of views in self-help groups and the development of an individual crisis network.

Atypical or typical depot preparations should be a treatment option when a patient expresses a preference for such treatment because of its convenience, or an essential part of a treatment plan in which the avoidance of covert non-adherence with antipsychotic drugs is a clinical priority (*Level D*). 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 (*Level D*). For optimum effectiveness in preventing relapse, depot preparations should be prescribed within the standard recommended dosage and interval range (*Level A*). 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. Randomised, control-group studies to determine the advantages of depot preparations of atypical neuroleptics compared to depots of typical neuroleptics are still needed. At the moment it can only be assumed that the advantages of atypical neuroleptics are also present in their depot formulation.

Special considerations in long-term treatment

Negative symptoms

Negative symptoms may often dominate the long-term course of schizophrenia and are more relevant for the outcome than positive symptoms. It is important for further therapeutic strategies to differentiate negative symptomatology into primary negative symptoms, and secondary negative symptoms as a consequence of positive symptoms (e.g., social withdrawal because of paranoid ideas), due to EPS (e.g., neuroleptic-induced akinesia), depressive symptoms (e.g., postpsychotic or pharmacogenic depression) or environmental factors (e.g., social understimulation due to hospitalism) (Carpenter et al. 1985). Treatment of schizophrenia

with predominantly negative symptoms was already described elsewhere (see Part 1 of these guidelines: acute treatment of schizophrenia, Falkai et al. 2005). Unfortunately most trials were carried out in patients experiencing acute exacerbations or presenting with a mixture of positive and negative symptoms, and therefore the improvement of negative symptoms could be interpreted at least partially as a decrease in secondary negative symptoms (Möller 2003). Relevant aspects for the efficacy of long-term treatment of negative symptoms are repeated in the following section.

Efficacy of first-generation antipsychotics. In most long-term studies there is improvement of negative symptoms with FGAs but the trials mainly focus on positive symptoms (Davis et al. 1989; Dixon et al. 1995) (*Level A*). There were no studies in patients with predominantly negative symptoms comparing FGAs with placebo.

Efficacy of second-generation antipsychotics. *Amisulpride* was associated with greater improvement in negative symptomatology compared to haloperidol in a 1-year, double-blind randomised maintenance study with flexible doses (Colonna et al. 2000). Selecting patients with predominantly negative symptoms, a randomised, double-blind, long-term trial comparing six dose levels of amisulpride with haloperidol revealed better, but no significantly superior improvement in negative symptoms after 1-year treatment in favour of amisulpride (Speller et al. 1997). Additionally, two short-term RCTs displayed better efficacy of amisulpride in the treatment of negative symptoms compared to placebo in a patient sample suffering predominantly from persistent negative symptomatology (Palliere-Martinot et al. 1995, Danion et al. 1999). In three small RCTs comparing amisulpride with FGAs in patients with predominantly negative symptoms (Pichot and Boyer 1989; Speller et al. 1997), there was only a trend in favour of amisulpride but no statistical difference. Nevertheless, with respect to the placebo-controlled studies there is evidence that treatment with amisulpride is effective in improving negative symptoms at a dose range of 50–300 mg/day in long-term outcome (*Level A*).

Aripiprazole demonstrated superior efficacy in improvement of negative symptoms over 6 months in a placebo-controlled RCT (Pigott et al. 2003). Pooled data of two 52-week RCTs comparing aripiprazole 30 mg/day to haloperidol 10 mg/day showed superior improvement in negative symptomatology in favour of aripiprazole (Kasper et al. 2003). In summary, although there is evidence for efficacy in treating negative symptoms in the

long-term course (*Level A*), there is no clear experience with aripiprazole in patients with predominantly negative symptoms.

Clozapine was found to be effective in open, non-comparative (short-term) trials in treatment refractory patients mostly suffering from long-term chronic schizophrenia with more or less predominant negative symptoms (Meltzer et al. 1989; Lindenmayer et al. 1994), superior in a double-blind trial compared to chlorpromazine (Kane et al. 1988), not significantly superior to haloperidol in one study (Breier et al. 1994), but clinically modestly superior in a more recent short-term double-blind multic comparative RCT clozapine (Volavka et al. 2002). In an open prospective study over 6 months (Spivak et al. 2003) and a double-blind trial over 12 months (Rosenheck et al. 1998), clozapine revealed superiority in reducing negative symptoms compared to haloperidol. While one meta-analysis found that there is slight significant evidence for superiority of clozapine compared to FGAs in the treatment of negative symptoms (Wahlbeck et al. 1999), another meta-analytic review reported an advantage of clozapine in this regard evaluating its efficacy in treatment-resistant patients (Chakos et al. 2001), both mostly evaluating short-term studies. In summary, although there is evidence for efficacy in treating negative symptoms (*Level A*), there is no experience with clozapine in patients with predominantly negative symptoms and only little experience treating negative symptoms over a long-term course.

Olanzapine displayed efficacy in treating negative symptoms in a 24-week extension study, but there was no statistically significant difference between olanzapine and haloperidol in reducing negative symptoms (Hamilton et al. 1998). A path-analysis of acute-phase studies found that most of the changes in negative symptoms could not be explained by other compounds (positive symptoms, depression, EPS) (Tollefson et al. 1997). One 28-week RCT demonstrated superiority of olanzapine (mean dose 17.2 mg/day) in improving negative symptoms compared to risperidone (mean dose 7.2 mg/day) (Tran et al. 1997). In summary, although there is evidence for efficacy in treating negative symptoms (*Level A*), there is no clear experience with olanzapine in patients with predominantly negative symptoms, and only limited experience in treating negative symptoms over a long-term course (*Level B*).

Quetiapine produced significantly superior improvement in negative symptoms compared to placebo in acute-phase RCTs (Arvanitis et al. 1997; Small et al. 1997). Quetiapine showed improvement of symptoms and continued efficacy in open trials in long-term treatment including negative

symptomatology (Buckley 2004; Cheer and Wagstaff 2004; Kasper et al. 2004), and comparable efficacy, e.g., to risperidone (Mullen et al. 2001). Overall, there is very limited evidence for efficacy of quetiapine in the treatment of negative symptoms in the long-term course (*Level C*).

Risperidone showed superior efficacy on negative symptomatology compared to haloperidol in a maintenance study (Csernansky et al. 2002) and inferior efficacy compared to olanzapine (Tran et al. 1997). A meta-analysis of the pooled results from six double-blind acute-phase RCTs comparing risperidone to FGAs found that risperidone showed significantly superior improvement in negative symptoms (Carman et al. 1995), and there is evidence from multiple open, long-term studies for the efficacy of risperidone in treating negative symptomatology. In summary there is evidence for efficacy in treating negative symptoms (*Level B*), but no clear experience in patients with predominantly negative symptoms.

Ziprasidone showed significantly superior improvement of negative symptoms compared to placebo in a double-blind, randomised, extension study over 1 year including patients with chronic schizophrenia presenting predominantly negative symptoms (dosage 40, 80 and 160 mg/day) at endpoint (Arato et al. 2002). In summary there is limited evidence for efficacy in treating negative symptoms over long-term course and in patients with predominantly negative symptoms (*Level C*).

Zotepine revealed inconsistent efficacy in achieving superior improvement of negative symptoms compared to FGAs in acute-phase RCTs (Möller 2003). A placebo-controlled study in patients with predominant negative symptoms failed to demonstrate efficacy of zotepine (Möller et al. 2004). A relapse-prevention, double-blind RCT displayed no significant differences compared to placebo with respect to negative symptomatology over 26 weeks (Cooper et al. 2000). In summary, there is no evidence for efficacy of zotepine in treating negative symptoms over the long-term course and in patients with predominantly negative symptoms.

Efficacy of antidepressive agents. Antidepressants are used as adjunctive treatment to atypical antipsychotic agents in patients with predominantly negative symptoms (APA 2004). The role of this strategy still remains unclear because the available studies (most of them performed with selective serotonin reuptake inhibitors, SSRIs) are inconsistent and often lack high methodological standards (Siris 2003; Möller 2004b). An earlier RCT indicated, for example, that imipramine added to long-acting FGAs may provide benefits in negative symptoms in stable outpatients

(Siris et al. 1991). Marprotiline revealed no significant difference in a double-blind crossover study (Waehrens and Gerlach 1980). In six placebo-controlled studies of SSRIs for negative symptoms, one reported a modest advantage of fluoxetine 20 mg/day added to long-acting injectable antipsychotic medication (Goff et al. 1995), and another reported significantly superior improvement in negative symptoms with fluoxetine (Spina et al. 1994), while four found no advantage for SSRIs, compared with placebo, in patients receiving fluoxetine combined with ongoing clozapine (Buchanan et al. 1996), and fluoxetine (Arango et al. 2000), citalopram (Salokangas et al. 1996), or sertraline (Lee et al. 1998) added to FGAs. Four controlled studies of adjunctive fluvoxamine (100 mg/day) found positive results (Silver and Nassar 1992; Silver and Shmugliakov 1998; Silver et al. 2000, 2003), while there was no benefit for marprotiline (100 mg/day) added to antipsychotic treatment (Silver and Shmugliakov 1998). In a double-blind, placebo-controlled study mirtazapine demonstrated superior improvement in negative symptomatology after 6 weeks (Berk et al. 2001). In contrast, reboxetine (8 mg/day) showed no effects on negative symptoms in a double-blind, placebo-controlled trial (Schutz and Berk 2001). Overall, the evidence for efficacy of antidepressants in treating negative symptoms of schizophrenia is limited (*Level C*), especially when taking into consideration the fact that in some cases it is difficult to differentiate the improvement in depressive symptoms from negative symptoms. Since most of the studies were performed in combination with FGAs, it is possible that the findings might be different with SGAs, although this possibility seems unlikely (APA 2004).

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

Recommendations. SGAs should be preferred for the treatment of negative symptoms in the long-term course (*Level A*). Of the atypical compounds, amisulpride demonstrated advantages in patients

with predominantly negative symptoms (*Level A*), but there is only limited experience in long-term treatment. In cases of inadequate response comedication with SSRIs (*Level B*) and possibly mirtazapine (*Level C*) may be beneficial. The pharmacokinetic interactions with SSRIs have to be considered carefully. Add-on therapies with glutamatergic agents or oestrogen may be discussed as experimental approaches.

Cognitive symptoms

Neurocognitive deficits have been recognised as an important feature, or even a core deficit, of schizophrenia. Cognitive functioning is a correlate of global and specific functional outcome in schizophrenia, and cognitive impairments account for significant variance in measures of functional status (Green 1996). SGAs have been reported to have more beneficial effects on cognitive functioning than FGAs, although the methodology used to assess cognitive deficits in schizophrenia has been deficient in many clinical studies (Harvey and Keefe 2001). The improvement of neurocognitive deficits is considered as a major target of long-term treatment, with growing importance in the last years.

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

randomised double-blind study demonstrated comparable cognitive-enhancing effects relative to previous treatment (mostly haloperidol or risperidone) in acutely ill inpatients treated with olanzapine or ziprasidone (Harvey et al. 2004).

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

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

Depressive symptoms

Depressive symptoms may occur in all phases of schizophrenia, especially as postpsychotic depression, and may contribute to the residual symptoms of schizophrenia, whereby the proportion of patients with schizophrenia who also manifest depression ranges from 7 to 75% (Siris 2000). Depressive symptoms have to be distinguished from side effects of antipsychotic medications (including medication-induced dysphoria, akinesia and akathisia), and the primary negative symptoms of schizophrenia (APA 2004). Some FGAs (e.g., thioridazine) (Dufresne et al. 1993) and SGAs are discussed as being effective in treating depressive symptoms in schizophrenia. It is suggested that SGAs are superior to FGA in this regard; however, evidence is limited (e.g., Tollefson et al. 1998; Peuskens et al. 2000; Möller 2005a,b). Treatment with antidepressants added as an adjunct to antipsychotics is indicated when the symptoms meet the syndromal criteria for a major depressive disorder or are severe and causing significant distress (e.g., when accompanied by suicidal ideation) or interfering with function (DGPPN 1998; APA 2004; Möller 2005c). Tricyclic antidepressants (TCAs) have been primarily examined in the treatment of postpsychotic depression (Siris et al. 2000) (*Level B*). Other antidepressants, e.g., SSRIs and dual reuptake inhibitors, have also been found to be useful in the treatment of depression in schizophrenia (Siris 2000) (*Level B*). Nevertheless, one RCT

observed no significant advantage with sertraline compared to placebo and demonstrated high placebo response (Addington et al. 2002). A small RCT comparing sertraline and imipramine in postpsychotic depression revealed comparable efficacy, but more rapid onset with sertraline (Kirli and Caliskan 1998). However, very few studies have examined the effects of antidepressants in patients treated with SGA, making it difficult to evaluate the current utility of adjunctive antidepressant agents. When prescribed, antidepressants are used in the same doses that are used for treatment of major depressive disorder (APA 2004). There are, however, potential pharmacokinetic interactions with certain antipsychotic medications; for example, the SSRIs (such as fluoxetine, paroxetine and fluvoxamine) are inhibitors of cytochrome P450 enzymes and thereby increase antipsychotic plasma levels. Similarly, the blood levels of some antidepressants may be elevated by the concomitant administration of antipsychotic medications.

Recommendations. When depressive symptoms meet the syndromal criteria for major depressive disorder or are severe and causing significant distress, treatment with antidepressants added as an adjunct to antipsychotics is indicated. Antidepressive agents, e.g., SSRIs, dual reuptake inhibitors or tricyclic antidepressants (TCAs) have been found to be effective in the treatment of depression in schizophrenia (*Level B*) and should be selected due to the presented profile of depressive symptomatology (e.g., concomitant agitation and insomnia versus apathy and loss of energy), pharmacological interactions and relevant side effects.

Quality of life

Besides the improvement in psychopathology and social function, optimisation of individual patients' subjective well-being and quality of life should be one of the major goals in the management of schizophrenia. As there is still a lack of agreement on the definition of the term quality of life, this construct is subjective in nature. A number of instruments (e.g., Subjective Well-being under Neuroleptic Treatment (SWN) scale, Quality of Life (QLS) scale, Sickness Impact Profile (SIP), Medical Outcomes Study Short-Form 36-item questionnaire (SF-36)) have been developed to measure quality of life aspects in an individual patient under neuroleptic treatment. Until now only a few randomised controlled studies have reported on the impact of antipsychotics on quality of life. The use of different measurement instruments limits a reliable comparative analysis (Awad and Voruganti 2004).

Efficacy of first-generation and second-generation antipsychotics. A randomised, open-label study showed superior improvement in quality of life (QLS, Social Functioning Scale) under treatment with *amisulpride*, compared to haloperidol or placebo (Saleem et al. 2002). A randomised open study comparing amisulpride and haloperidol revealed similar results (Colonna et al. 2000). In a double-blind, 16-week trial, quality of life (QLS, Functional Status Questionnaire) improved to a significantly greater extent under amisulpride compared to haloperidol (Carriere et al. 2000). There was no difference in improvement of quality of life between amisulpride and olanzapine in a 6-month randomised, double-blind study (Mortimer et al. 2004).

An open-label study comparing *clozapine* with FGAs in treatment-resistant patients found similar improvement in quality of life aspects (Essock et al. 1996b). In a randomised, double-blind, 1-year follow-up study, treatment-refractory patients demonstrated significantly superior improvement in quality of life (QLS), had better medication adherence and were more likely to participate in psychosocial rehabilitation programmes with clozapine compared to haloperidol (Rosenheck et al. 1997, 1998, 1999b).

Olanzapine-treated patients in the medium (7.5–12.5 mg/day) or high (10–20 mg/day) dose group showed significant improvement in quality of life (QLS) compared to haloperidol and placebo after 24 weeks of treatment in a randomised double-blind acute phase trial (Hamilton et al. 1999). This result could be replicated in two randomised, double-blind multicentre studies with a long-term extension phase, whereas olanzapine-treated patients experienced superior improvement in quality of life (QLS, SF-36) compared to haloperidol in the acute phase, and continuing improvement in the extension phase (Revicki et al. 1999; Hamilton et al. 2000). In contrast, a randomised, double-blind trial lasting 12 months found no advantage for olanzapine compared to haloperidol (Rosenheck et al. 2003). Olanzapine was non-inferior to clozapine in the improvement of quality of life (SWN, Munich Quality of Life Dimension List) in a recent randomised, double-blind multicentre trial (Naber et al. 2005). Elderly schizophrenic patients switched from FGAs to olanzapine showed a better response than those switched to risperidone on the psychological domain of the WHO-Quality of Life (Brief) scale in a randomised open-label study (Ritchie et al. 2003). In a randomised, double-blind trial over 30 weeks, olanzapine-treated patients experienced significantly more improvement in some aspects of quality of life (QLS, SF-36) compared to risperidone (Gureje et al. 2003).

Cross-sectional data demonstrated the superiority of *quetiapine* compared with FGAs for improving quality of life, and a long-term switch study showed comparable improvement of quality of life between *quetiapine*, *risperidone* and *olanzapine* (Awad and Voruganti 2004).

A randomised, double-blind study showed similar improvement in quality of life compared to baseline in *risperidone*- and *olanzapine*-treated schizophrenic patients measured by the QLS (Tran et al. 1997). In a randomised, controlled trial, patients receiving *risperidone* demonstrated significantly greater improvement in quality of life, measured by the SF-36 and the Quality of Life Interview (QoLI), than patients receiving FGAs (Mahmoud et al. 1999). A single-blind, naturalistic, cross-sectional study of stabilised patients comparing *risperidone*, *olanzapine*, *clozapine* and *quetiapine* with FGAs revealed greater improvement in self-rated but not clinician-rated quality of life in patients treated with the SGAs (Voruganti et al. 2000). A single-blind naturalistic study in which patients were switched from FGAs to either *risperidone*, *olanzapine* or *quetiapine* showed significant improvement in several aspects of quality of life at 1-year follow-up (Voruganti et al. 2002). No significant difference in subjective quality of life (EuroQol-Visual Analogue Scale) could be detected in a double-blind trial comparing *flupenthixol* and *risperidone*, while the ability to cope with stress, to achieve something and to feel relaxed improved significantly more in the *flupenthixol* group (Hertling et al. 2003).

Zotepine improved the quality of life (Munich Quality of Life Dimension) more than FGAs but less than *clozapine* and *risperidone* in an open-label, cross-sectional study with a small sample size (Franz et al. 1997), and revealed superiority in improving quality of life compared to placebo (SF-36) in an 8-week randomised, double-blind trial (Möller et al. 2004). Long-term trials with *zotepine* with respect to quality of life parameters are not available.

Recommendations. Although some studies are inconclusive and their results are inconsistent there is a clear trend indicating superiority for *amisulpride* (*Level B*), *clozapine*, *olanzapine* and *risperidone* (*Level A*), *zotepine* (*Level B*) and *quetiapine* (*Level C*) compared to FGAs in improving quality of life. Data concerning quality of life parameters during long-term treatment are only available for *amisulpride* (*Level B*), *clozapine*, *olanzapine* and *risperidone* (*Level A*), and very limited for *quetiapine* (*Level C*). In summary, the mentioned studies may be an additional argument to prefer SGAs with respect to quality of life aspects.

Other biological treatment strategies

Electroconvulsive therapy (ECT)

The evaluation preceding electroconvulsive therapy (ECT), procedure, application and overall efficacy of ECT were described previously (see Part 1 of these guidelines: acute treatment of schizophrenia, Falkai et al. 2005). Although findings in patients with depression suggest that unilateral and perhaps bifrontal electrode placement may be associated with fewer cognitive effects, and that efficacy with unilateral electrode placement may depend on the extent to which the stimulus intensity exceeds the seizure threshold, the applicability of these observations to patients with schizophrenia is uncertain (APA 2004). One result of meta-analyses and HTA reports concerning the efficacy of ECT in patients with chronic schizophrenia is that antipsychotic treatment alone generally produces better short-term outcomes compared with ECT alone (e.g., APA task force 2001; Tharyan and Adams 2004) (*Level A*). There is also evidence from at least three studies that ECT leads to a significantly better global impression compared to sham (placebo) treatment (Thayran and Adams 2004) (*Level A*). Nevertheless, there are different opinions and other reviewers did not find a significant advantage for ECT compared with sham treatment regarding mental state (APA 2004). Combined treatment with ECT and first-generation antipsychotic medications (FGAs) was observed to be more effective than treatment with ECT alone in most but not all studies (APA 2004). There are no studies with large sample sizes available to prove the long-term efficacy of ECT.

In summary, apart from catatonia, electroconvulsive therapy (ECT) should only be used in exceptional cases in treatment-refractory schizophrenia, as no advantages have been consistently demonstrated compared with pharmacological treatments (*Level C*). Most studies of ECT did not conduct a comparison to monotherapy with atypical agents as an alternative. ECT should be considered in patients suffering from severe affective symptoms, as there is limited evidence in trials and clinical knowledge to confirming its efficacy in such cases (APA 2004; Tharyan and Adams 2004) (*Level C*).

Repetitive transcranial magnetic stimulation (rTMS)

Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive technique stimulating cortical neurons by magnetic induction using a brief, high-intensity magnetic field. This novel somatic technique has been studied in many neuropsychiatric diseases, but to date it is not an approved treatment

for neuropsychiatric disorders (Burt et al. 2002). For schizophrenia, target symptoms of rTMS have been persisting auditory hallucinations and negative symptoms. In these studies, repetitive transcranial magnetic stimulation (rTMS) was applied as an adjuvant therapy to ongoing antipsychotic treatment.

Improvement in auditory hallucinations after stimulation of the left temporal-parietal cortex augmenting antipsychotic treatment was observed in two randomised, double-blind, sham (placebo)-controlled trials and in one randomised, double-blind, cross-over study, each with small sample sizes (Hoffman et al. 2000; Hoffman et al. 2003; Poulet et al. 2005). Two other randomised, sham-controlled trials could not confirm these positive results, and found no significant differences between sham and verum stimulation (McIntosh et al. 2004; Schoenfeldt-Lecuona et al. 2004).

In a randomised, double-blind, sham-controlled study in 35 patients with schizophrenic or schizoaffective psychoses with low-frequency rTMS over the right prefrontal cortex, no significant group differences except for the use of mood stabilisers in four participants of the verum group could be detected (Klein et al. 1999). In a randomised, double-blind sham-controlled study high-frequency rTMS over the left dorsolateral prefrontal cortex (DLFPC) resulted in significant improvement compared to sham stimulation in the average BPRS score in 12 schizophrenic patients (Rollnik et al. 2000; Huber et al. 2003). Another study displayed a trend for a temporary improvement immediately after the application of a single verum 20 Hz rTMS session, persisting until the following day (Nahas et al. 1999). This was underlined by a study which reported a significant improvement in negative symptoms in 20 schizophrenic patients treated with 10 Hz high-frequency rTMS compared to sham stimulation (Hajak et al. 2004). In contrast to these encouraging results, a recently published study showed no significant effect of 10 Hz rTMS over left dorsolateral prefrontal cortex in 22 chronically hospitalised schizophrenic patients compared to sham (Holi 2004). The severity of disease and dosage of medication were discussed as possible explanations for the missing effect. In addition to the randomised, sham-controlled studies mentioned above, three open clinical trials and one case report demonstrated up to 33% improvement in negative symptoms with high-frequency rTMS over left prefrontal cortex (Cohen et al. 1999; Rollnik et al. 2001).

In summary, high-frequency rTMS seems to be a promising technique to improve negative symptoms in schizophrenia (*Level B*), although its efficacy has

to be proven in randomised, controlled trials with larger sample sizes. Results for applying low-frequency rTMS to reduce persisting auditory hallucinations are inconsistent.

Management of relevant side effects

Antipsychotic medications are associated with differing risks of a variety of side effects, including neurological, metabolic, sexual, endocrine, sedative and cardiovascular side effects. These side effects may have an even greater influence on the choice of medication in the long-term than in the acute phase 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 weight gain, extrapyramidal symptoms (EPS) (especially tardive dyskinesia), and 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. 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. SGAs have clear advantages with respect to EPS (especially tardive dyskinesia) and may have advantages in improving cognitive deficits, negative and depressive symptoms, subjective well-being and quality of life compared to FGAs. These advantages have to be weighed against other side effects, e.g., a higher risk of weight gain and diabetes mellitus with some agents. An 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 recommended in the following section. A short overview of therapeutic options for managing relevant side effects is given in Tables III and IV.

Neurological side effects

Extrapyramidal side effects. Extrapyramidal side effects can be divided into acute (acute dystonic reactions, parkinsonism, akathisia) and chronic (akathisia, 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 reactions. Acute dystonic reactions respond dramatically to the administration of

Table III. Therapeutic options to manage antipsychotic side effects.

Side effect	Prevention	Treatment
<i>EPS</i>		
Acute dystonic reactions	<ul style="list-style-type: none"> – Select SGA with low rate of EPS – Start with low dose – Increase dose slowly and stepwise 	<ul style="list-style-type: none"> – Oral or intravenous application of anticholinergic drug, e.g., 2.5–5 mg biperiden, if necessary repeat procedure after 30 minutes, continue biperiden oral (maximal 12 mg/day) – Switch to SGA
Parkinsonism	<ul style="list-style-type: none"> – Select SGA – Increase dose slowly and stepwise 	<ul style="list-style-type: none"> – Dose reduction – Oral application of anticholinergic drug (e.g., biperiden 4–12 mg/day) – Switch to SGA
Akathisia	<ul style="list-style-type: none"> – Select SGA – Increase dose slowly and stepwise 	<ul style="list-style-type: none"> – Dose reduction – 1. Oral application of β-blocking agent (e.g., propranolol 30–90 mg/day) – 2. Oral application of benzodiazepines (e.g., diazepam) – 3. Try anticholinergic drug (e.g., biperiden, max. 12 mg/day) – Switch to SGA
Tardive dyskinesia	<ul style="list-style-type: none"> – Select SGA – Evaluate risk factors for TD – Supplementing vitamin E 	<ul style="list-style-type: none"> – Switch to clozapine (alternatively to other SGA, e.g., olanzapine, quetiapine, aripiprazole) – Oral application of tiapride – Oral application of baclofen (20–120 mg/day) or valproate (500–1200 mg/day) – Try supplementing with vitamin E (400–1600 IE/day)
<i>NMS</i>		
Neuroleptic malignant syndrome	<ul style="list-style-type: none"> – Select SGA 	<ul style="list-style-type: none"> – 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 – Alternatively bromocriptine, lisurid, amantadine or clonidine – In single cases ECT

anticholinergic or antihistaminic medication (APA 1997). Parenteral administration will have a more rapid onset of action than oral administration. Clozapine and newer atypical agents do not appear to trigger acute dystonia. A lower dose of typical antipsychotic medications and prophylactic administration of anticholinergic agents are thought to reduce the risk of acute dystonia.

Parkinsonism. Antipsychotic-induced parkinsonism generally resolves after discontinuation of antipsychotic medication, 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 atypical antipsychotic medications. If this is not possible, administration of anticholinergic agents or dopamine agonists should be considered. However, dopamine agonists 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.

Akathisia. Several strategies have been used to decrease akathisia. There is no randomised, controlled trial which provides evidence for the use of anticholinergic drugs for treatment of akathisia. Should a person suffer from distressing akathisia despite other treatment strategies, a trial of an anticholinergic drug may be warranted (Lima et al. 2004). Benzodiazepines (clonazepam oral 0–2.5 mg/day) were used in two studies (RCT) to reduce akathisia (Kutcher et al. 1989; Pujalte et al. 1994). Treatment of akathisia consists of a dose reduction or administration of β -blockers. In contrast to clozapine, the newer atypical antipsychotic medications are far less likely to trigger akathisia. They are thus the drugs of choice in intolerable akathisia

Table IV. Therapeutic options to manage antipsychotic side effects.

Side effect	Prevention	Treatment
Weight gain	<ul style="list-style-type: none"> – Selecting antipsychotic with lower risk of weight gain 	<ul style="list-style-type: none"> – Dietary supplementation, physical activity – CBT or psychoeducation – Switching to another antipsychotic – Adding an H₂-receptor blocker (e.g., nizatidine, ranitidine) – Combine with topiramate
Hyperlipidemia	<ul style="list-style-type: none"> – Screening for risk factors, cholesterol and triglycerides (TG) – Selecting antipsychotic with low risk of inducing hyperlipidemia 	<ul style="list-style-type: none"> – Dietary management, weight reduction – Specific pharmacological treatment (e.g., cholesterol and TG reducer) – Switching to an antipsychotic with lower risk of hyperlipidemia
Diabetes	<ul style="list-style-type: none"> – Screening for diabetes risk factors, fasting blood glucose, in some cases haemoglobin A1c – Selecting antipsychotic with low risk of inducing diabetes 	<ul style="list-style-type: none"> – Dietary management – Referring to a diabetologist for special pharmacological treatment of diabetes – Switching to an antipsychotic with lower risk of diabetes
Orthostatic hypotension	<ul style="list-style-type: none"> – Starting with low dose, increase dose slowly and stepwise – Selecting antipsychotic with low α-adrenergic receptor-blocking profile 	<ul style="list-style-type: none"> – Physical activity – Application of oral dihydroergotamine (max. 6 mg/day) or etilefrine (20–60 mg/day) – Switching to other antipsychotics (due to receptor profile)
QTc prolongation	<ul style="list-style-type: none"> – Selecting antipsychotic with low risk of QTc prolongation – Evaluation of cardiac risk factors – Control for pharmacological interactions – Control of ECG 	<ul style="list-style-type: none"> – If QTc >480–520 ms or has increased more than 60 ms switching to another antipsychotic is indicated
Dry mouth	<ul style="list-style-type: none"> – Prescribing low doses – Selecting antipsychotic with lower risk 	<ul style="list-style-type: none"> – Drinking small amounts frequently – Using sugarfree drops or chewing gum – Dose reduction
Sialorrhea	<ul style="list-style-type: none"> – Selecting antipsychotic with lower risk 	<ul style="list-style-type: none"> – Application of pirenzepine 25–50 mg/day – Dose reduction (e.g., of clozapine)
Sexual dysfunction	<ul style="list-style-type: none"> – Selecting antipsychotic with no or minimal prolactin elevation. Evaluating prolactin level 	<ul style="list-style-type: none"> – Switching to another antipsychotic with lower risk of prolactin elevation
Constipation	<ul style="list-style-type: none"> – Selecting antipsychotic with lower risk 	<ul style="list-style-type: none"> – Dietary supplementation, physical activity – Lactulose 5–10 g/day, or macrogol 13–40 g/day, or natriumpicosulfat 5–10 mg/day
Urinary retention	<ul style="list-style-type: none"> – Selecting antipsychotic with low anticholinergic side effects 	<ul style="list-style-type: none"> – Dose reduction – Switching to another antipsychotic – Application of carbachole 1–4 mg/day orally; if necessary 0.25 mg i.m. or s.c. – Application of distigmine 2.5–5 mg/day orally
Leukopenia	<ul style="list-style-type: none"> – Controlling white blood cell count (WBC) 	<ul style="list-style-type: none"> – 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 <3500 or granulocytes <1500

occurring with typical antipsychotic medications. Effective treatments for akathisia include centrally acting β -blockers, such as a low dose of propranolol (30–90 mg/day) (Fleischhacker et al. 1990). When these medications are administered, blood pressure and pulse rate should be monitored with dose changes. Benzodiazepines such as lorazepam and clonazepam are also effective in decreasing symptoms of akathisia (APA 1997).

Tardive dyskinesia. Administration of clozapine is recommended in severe forms, as an antidyskinetic effect of this agent is under discussion, as well as the possible avoidance of further risk accumulation. No randomised, controlled trial-derived data were available to clarify the role of neuroleptics as treatments for tardive dyskinesia (TD). This includes the newer atypical antipsychotics and clozapine, although there is some preliminary evidence derived from non-randomised, controlled trials that clozapine is an effective treatment for TD (McGrath and Soares-Weiser 2004). Despite the fact that neuroleptic cessation is frequently a first-line recommendation, there were no RCT-derived data to support this (McGrath and Soares-Weiser 2004). Two studies found a reduction in TD associated with neuroleptic reduction (Kane et al. 1983; Cookson 1987), although the risk of psychotic relapse should be taken into consideration when lowering the neuroleptic dose (Gilbert et al. 1995).

The use of cholinergic agents like lecithin, deanol or meclofenoxate for treatment of neuroleptic-induced tardive dyskinesia is not recommended because of the lack of evidence and due to adverse effects (Tammenmaa et al. 2004). There is no compelling evidence that benzodiazepines decrease tardive dyskinesia in a sufficient manner (Walker and Soares 2004). The two randomised, controlled trials with small sample sizes showed no clinically relevant advantage for benzodiazepines (diazepam mean dose 12–48 mg/day and alprazolam mean dose 7.2 mg/day) compared with no treatment on top of standard care or placebo (Weber et al. 1983; Csernansky et al. 1988).

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).

A tendency for reduced TD symptoms was reported for treatment with GABA-agonist drugs (baclofen, progabide 20–40 mg/kg per day, sodium valproate 500–1200 mg/day, or tetrahydroisoxazopyridine, THIP), but a clinically important

improvement (reduction of more than 50% on any TD scale) could not be demonstrated in three randomised, controlled trials compared with placebo (Soares et al. 2004). In cross-over trials a significant improvement was reported in two studies with baclofen 20–120 mg/day (Gerlach et al. 1978; Ananth et al. 1987), one with sodium valproate 900 mg/day (Linnoila 1976) and one with THIP 60–120 mg/day (Thaker et al. 1987), but these trials also showed a range of moderate to severe side effects. In one cross-over study neither improvement nor side effects with baclofen up to 90 mg/day during the follow-up period were described (Nair et al. 1978).

Small trials with uncertain quality of randomisation indicate that vitamin E protects against deterioration of TD but there is no evidence that vitamin E improves symptoms of TD (Soares and McGrath 2004).

Recommendations. Acute dystonic reactions should be treated with anticholinergic medication (*Level D*). If severe, and in case of emergency, anticholinergics should be administered parenterally. To avoid severe antipsychotic-induced parkinsonism, lower doses of FGAs are recommended and treatment may consist of FGA dose reduction. Antipsychotic-induced parkinsonism could be treated effectively with anticholinergic medication (*Level D*). Akathisia could be treated with β -blocking agents (e.g., propranolol), including cardiovascular monitoring, or with benzodiazepines (*Level C*). For tardive dyskinesia, switching to clozapine may be the most effective treatment (*Level A*), or if not possible neuroleptic dose reduction is recommended (*Level B*).

Neuroleptic malignant syndrome. Neuroleptic malignant syndrome (NMS) is characterised by dystonia, rigidity, fever, autonomic instability such as tachycardia, delirium, myoglobinuria and increased levels of creatine kinase, leukocytes and hepatic enzymes. If malignant neuroleptic syndrome (MNS) occurs, antipsychotic treatment should immediately be terminated, vital functions stabilised under close monitoring and hyperthermia adequately treated. Despite general treatment options, specific pharmacological or somatic treatments may be considered. Electroconvulsive therapy (ECT) provides some benefit, but randomised controlled studies are lacking (Supprian 2004).

Dantrolen showed success (dosage 2.5–10 mg/kg body weight daily, intravenously applied) and provided the greatest reduction in mortality compared to the treatment with bromocriptine and amantadine (Sakkas et al. 1991). There are several case reports for successful treatment with

amantadine in doses of 200–400 mg/day (Susman 2001). Dopaminergic agents, e.g., *L-Dopa* itself, in combination with and without carbidopa and apomorphine show some efficacy in treating NMS in case reports (Wang and Hsieh 2001). Case reports recommend the use of *bromocriptine* in doses of 7.5–45 mg/day (Susman 2001). *Lisurid* was also reported to be effective and may have some advantages compared to bromocriptine, because it can be administered additionally intravenously and subcutaneously. *Benzodiazepines* are recommended traditionally and were used particularly if MNS could not be distinguished from catatonia ('catatonic dilemma'). Especially in less severe cases there were no adverse effects when treatment with benzodiazepines was initiated, e.g., lorazepam in doses of 4–8 mg/day was recommended (Susman 2001). Treatment with *clonidine* demonstrated success and improved the course of NMS (e.g., reduced stay in an intensive care unit) (Gregorakos et al. 2000). Administration of *anticholinergics* was reported to be beneficial, but may cause hyperthermia itself. Therefore anticholinergics are not recommended in the treatment of NMS (Caroff et al. 2000).

Treatment with *ECT* demonstrated efficacy in NMS in open studies and case reports (Davis et al. 1991) compared to a control group. Prior to ECT an attempt with dantrolene may be useful (Nisijima and Ishiguro 1999). After the treatment of NMS, reintroduction of antipsychotic therapy is recommended, whereby an atypical agent not relevantly associated with a risk of NMS should be preferred.

Recommendations. NMS needs intensive care management with monitoring of vital signs. If NMS is suspected, antipsychotic treatment should be stopped and benzodiazepines should be administered (*Level D*). In case of a probable or clinically defined NMS, additional treatment with dantrolene should be initiated and, if there is no improvement of symptoms, ECT should be considered (*Level C*).

Epileptic seizures. Epileptic seizures occur in an average of 0.5–0.9% of patients receiving antipsychotic medications, whereby treatment with clozapine and zotepine is dose-dependently associated with the highest incidence rate (up to 17%). Seizures can be effectively treated with benzodiazepines, as well as anticonvulsant agents such as phenytoin or valproic acid (APA 1997). 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.

Cognitive side effects. Although antipsychotic medications can effectively improve *cognitive functions* in schizophrenic patients, memory problems and cognitive disorders represent possible side effects of antipsychotic therapy, which are particularly associated with the anticholinergic effect of antipsychotic medications and the use of anticholinergic agents such as biperiden. Drug-induced cognitive disorders have been more frequently reported during treatment with typical antipsychotic medications (Harvey and Keefe 2001).

Sedation is a common side effect of FGAs, as well as of several SGAs, and may be related to antagonist effects of those drugs on histaminergic, adrenergic and dopaminergic receptors. Sedation occurs more frequently with low-potency typical antipsychotic medications and clozapine. Sedation is most pronounced in the initial phases of treatment, since most patients develop some tolerance to the sedating effects with continued administration. Lowering of the daily dose, consolidation of divided doses into one evening dose, or changing to a less-sedating antipsychotic medication may be effective in reducing the severity of sedation. There are no systematic data on specific pharmacological interventions for sedation, but caffeine may be a relatively safe option. Some forms of psychostimulants (e.g., modafinil) have also been used to treat daytime drowsiness. However, there have been case reports of clozapine toxicity associated with modafinil and other stimulant treatments of sedation, and thus this drug combination should be carefully considered and used with caution. If anticholinergic treatment is required to prevent or improve EPS (e.g., under treatment with FGAs), and cognitive side effects may result from this treatment, switching to SGAs has to be considered.

Obesity and weight gain

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

Unfortunately the effectiveness of *psychological* interventions for weight loss in schizophrenic

patients seems to be low, although five earlier dietary and cognitive behaviour trials pre-dating the availability of SGAs suggested that patients with mental illness may change their lifestyle and display weight loss (Birt 2003). Factors affecting management of weight gain are negative symptoms, cognitive impairment, low income level, preference of high-calorie food, impaired satiety, level of sedation and reduced ability to handle daily hassles (e.g., shopping and cooking) (Sharpe and Hills 2003). In hospitalised, clozapine-treated patients with pre-existing physical or metabolic defects, dietary restriction led to mean weight loss of 7.1 kg in men and 0.5 kg in women compared to weight gain of 2.0 kg in men and 6.1 kg in women not dieting over 6 months (Heimberg et al. 1995). In a residential setting, a low-fat, low-calorie diet was not able to change average body weight over 2 years, but clozapine- and olanzapine-treated patients who gained weight were able to lose it during this nutrition counselling programme (Aquila and Emanuel 2000). A community-based educational programme failed to induce weight loss in patients with clozapine, whereas olanzapine-treated patients had some benefits (Wirshing et al. 1999b). In a small sample of olanzapine-treated outpatients, a Weight Watchers programme with 10 weekly sessions provided moderate weight loss in men, but rarely in women participating in this intervention (Ball et al. 2001). Successful reversal of antipsychotic-induced weight gain in 6 months was described in a sample of patients receiving a weight loss programme designed for the mentally ill with respect to dietary counselling, exercise programme and self-monitoring (Centorrino et al. 2002). The effectiveness of a multimodal intensive weight management programme consisting of exercise, nutrition and behavioural interventions could be demonstrated by significant weight loss and increase of nutrition knowledge at the 12-months outcome in patients receiving different atypicals compared to a matched control group (Menza et al. 2004). In a randomised, experimental design an intensive psychoeducational programme with weekly 1-hour sessions, focusing on nutrition and fitness, for a total of 4 months demonstrated superiority in preventing olanzapine-induced weight gain compared to standard care consisting of diet counselling and exercise (Littrell et al. 2003). A cognitive behavioural approach including seven to nine individual and 10 bi-weekly group sessions followed by six group sessions on weight maintenance led to a significant drop in mean body mass index in a small sample of clozapine- and olanzapine-treated outpatients, but long-term success was not assessed (Umbricht et al. 2001). A systematic review of behavioural interventions in

cases of antipsychotic weight gain, which included 13 studies, stated that calorie restriction in a controlled ward environment, structured counselling combined with CBT, counselling on life style and provision of rewards may potentially lead to weight loss. This result is limited due to the weak methodology used in the studies; furthermore, of seven trials with a control group only two yielded significant results (Werneke et al. 2003).

Although *pharmacological* approaches such as dosage reduction or switching to an SGA with a lower weight gain liability promise to be successful interventions for weight loss, this strategy has to be weighed against the potentially higher risk of relapse when changing an effective agent (Sharpe and Hills 2003). In an open, 8-week study, switching from other antipsychotics to *aripiprazole* resulted in significant weight loss (Casey et al. 2003b). In an open-label study including 12 psychiatrically stable schizophrenic, schizoaffective and bipolar patients displaying excessive weight gain with olanzapine, switching to *quetiapine* led to a decline in mean weight of 2.25 kg in 10 weeks (Gupta et al. 2004). In an open-label, parallel-group, 6-week trial, switching to *ziprasidone* led to a significant reduction of the mean body weight under risperidone (mean change 0.9 kg) and olanzapine (mean change 1.8 kg), but to a slight increase from FGAs (mean change 0.3 kg) in a large sample of stable outpatients with persistent symptoms or troublesome side effects (Weiden et al. 2003a,b). In all these studies no worsening of psychopathology was observed. In a non-psychiatric population specific drug therapy for obesity is recommended exclusively as part of an integral treatment plan in patients with a BMI above 30 kg/m², or in combination with obesity related risk factors or diseases with a BMI above 27 kg/m² (Zimmermann et al. 2003). There is one case report suggesting moderate weight loss after adding *orlistat*, a lipase inhibitor reducing intestinal fat absorption, to amisulpride (Anghelescu et al. 2000). An open study in 19 paediatric patients treated with olanzapine, risperidone, quetiapine or valproate revealed a decrease of mean body weight (2.9 kg after 12 weeks) after adding *metformine* 500 mg three times daily, an antidiabetic drug (Morrison et al. 2002). In contrast, no effect of metformine was reported in five patients on long-term treatment with haloperidol, fluphenazine, trifluoperazine or risperidone (Baptista et al. 2001). Weight reduction was reported with open-label add-on treatment of *amantadine* after 2 weeks in 10 patients taking FGAs (Correa et al. 1987). The effect of weight loss could be confirmed by 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), and in a double-blind, 16-week trial in 60 patients with schizophrenia, schizophreniform or bipolar disorder compared to placebo (Deberdt et al. 2005). Amantadine, a dopamine agonist, has a risk of worsening psychosis (Ananth et al. 2004). *Nizatidine*, a peripheral H₂-receptor blocker, which probably acts by inducing early satiety related to increased cholecystokinin and reduced production of gastric acid, has been reported to reduce weight gain in doses of 300 mg/day in a patient taking olanzapine (Sachetti et al. 2000). In 8-week, randomised, double-blind, placebo-controlled studies, nizatidine confirmed its weight-losing 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 nizatidine twice daily without presenting significant differences in adverse events (Cavazzoni et al. 2003), but the difference was not statistically significant at 16 weeks. 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). There have been four case reports published indicating that the anticonvulsant *topiramate* added to valproate, carbamazepine, quetiapine and olanzapine demonstrates benefits in weight loss (Birt 2003). In addition, 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). Cautious use in people with mental illness is warranted for anorecting agents like phentermine, chlorphentermine, sibutramine or phenylpropanolamine due to exacerbation of psychotic symptoms. For this reason these agents cannot be recommended in patients with schizophrenia. Furthermore, adding phentermine and chlorphentermine to patients with chlorpromazine-associated weight gain (Sletten et al. 1967) and phenylpropanolamine to clozapine therapy (Borovicka et al. 2002) failed to show any significant positive effects on weight gain.

Combination of fluoxetine (20 mg/day in one RCT and 60 mg/day in another RCT) with olanzapine demonstrated no significant weight loss or prevention of weight gain compared to placebo (Poyurovsky et al. 2002; Bustillo et al. 2003). In an RCT augmentation of *fluvoxamine* (50 mg/day) to clozapine (dosage up to 250 mg/day) revealed significantly less weight gain compared to clozapine monotherapy (dosage up to 600 mg/day), controlled

for similar clozapine levels in both groups (Lu et al. 2004). Add-on treatment with *reboxetine* led to a significant reduction of mean body weight in olanzapine-treated patients compared to placebo in a randomised, controlled study (Poyurovsky et al. 2003).

Recommendations. In summary, 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 (*Level C*). If this approach fails, it is appropriate to consider dose reduction of the current antipsychotic (*Level D*), or switching to another SGA with lower weight gain liability, e.g., ziprasidone, aripiprazole and quetiapine (*Level C*).

Metabolic side effects

Diabetes. There is evidence that schizophrenia itself is an independent risk factor for impaired glucose tolerance, which is a known risk factor for developing type 2 diabetes, regardless of whether patients receive antipsychotic medication (Ryan et al. 2003; Bushe and Holt 2004). The interactions between schizophrenia and diabetes are likely to be multifactorial and include genetic and environmental factors. Pharmacological studies revealed an association between diabetes and atypical antipsychotics. Although the studies are inconclusive, the highest risk is assumed for clozapine and olanzapine treatment (Marder et al. 2004). In consequence a baseline measure of (fasting) plasma glucose level should be collected for all patients before starting a new antipsychotic, or alternatively haemoglobin A_{1c} should be measured (Marder et al. 2004). Patients and their caregivers should be informed about the symptoms of diabetes, and patients should be monitored at regular intervals for the presence of these symptoms. The risks and consequences of 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.

Hyperlipidemia. Retrospective reports and pharmacoepidemiological studies found a significantly greater extent of elevations of lipids in patients taking certain atypical antipsychotic medications (especially olanzapine and clozapine) (e.g., Wirshing et al. 2002). Before and during antipsychotic treatment total cholesterol, low-density lipoprotein (LDL) and HDL cholesterol, and triglyceride levels should be measured (Marder et al. 2004). If the

LDL level is greater than 130 mg/dl the patient should be referred to an internist to evaluate whether treatment with a cholesterol-lowering drug should be initiated.

Other side effects

Hyperprolactinemia and sexual dysfunction. If hyperprolactinemia is suspected in a schizophrenic 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 tumor) (Marder et al. 2004). When antipsychotic-induced hyperprolactinemia 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. The treatment of choice is a switch of medication and administration of bromocriptine. Gynaecomastia and priapism are rare complications of antipsychotic therapy.

Cardiovascular side effects. 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 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 β -blocker (e.g., atenolol) (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 500 ms) is associated with an increased risk of torsade de pointes and transition to ventricular fibrillation. If this occurs under neuroleptic treatment, the medication should be discontinued and switched to an antipsychotic with

a lower risk of cardiac conduction disturbances (Marder et al. 2004). Case reports indicate that the use of clozapine is associated with a risk of *myocarditis* in 1 per 500 to 1 per 10,000 treated patients. If the diagnosis is probable, clozapine should be stopped immediately and the patient referred urgently to a specialist for internal medicine (Marder et al. 2004).

Haematological side effects. *Agranulocytosis* is the most severe side effect of clozapine and some other FGAs (e.g., chlorprothixen). In rare cases, however, the condition may also occur in association with other antipsychotic medications. During clozapine treatment, a white blood-cell (WBC) count $<2000/\text{mm}^3$ or absolute neutrophil count (ANC) $<1000/\text{mm}^3$ 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 $2000\text{--}3000/\text{mm}^3$ or ANC of $1000\text{--}1500/\text{mm}^3$ 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 $3000\text{--}3500/\text{mm}^3$ and the ANC is $>1500/\text{mm}^3$, the WBC count has to be repeated with a differential count twice a week until the WBC count is $>3500/\text{mm}^3$.

Others. *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 α -adrenergic agonist activity (Rabinowitz et al. 1996). 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 (APA 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). In studies involving olanzapine, reversible, mainly slight elevations in hepatic enzymes have been reported.

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 (APA 2004). As cataracts were observed in beagles that were given quetiapine, psychiatrists should ask about the quality of distance vision and about blurry vision, and should refer to an ocular evaluation 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 carbachole.

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 sugarfree chewing gum or drops against dry mouth. To treat constipation, patients should be advised to drink more, and in some cases administration of lactulose may be useful.

Usually patients mostly suffer from the described autonomic side effects when antipsychotic treatment is introduced or doses are increased.

Psychotherapy and psychosocial interventions in the context of long-term treatment

The target strategy in long-term treatment of schizophrenia should be a combination of long-term antipsychotic treatment and psycho- and sociotherapeutic procedures, so that the relapse rate is further reduced and the course of disease can be further improved (NICE 2002; APA 2004).

As mentioned earlier, these guidelines focus on biological (somatic) treatments of schizophrenia. Therefore psychotherapeutic and psychosocial approaches in combination with pharmacotherapy and their value in long-term treatment will only be summarised briefly. No systematic evaluation of their efficacy has been conducted and evidence-based recommendations are restricted to main topics regarding guidelines, meta-analysis and systematic reviews. Interventions related to special attitudes of care systems are not included because these options may strongly differ from culture

and country, and thus be difficult to summarise in international guidelines. Particularly after stabilisation, in the remission and stable phase, psychotherapeutic and psychosocial approaches may reveal the most benefit in the treatment of schizophrenia.

Psychotherapy

A number of psychological approaches have been introduced in long-term treatment. The aims of psychological treatment methods in schizophrenic disorders are to enhance coping with stress, alleviate the adverse influence of external stressors, improve the quality of life, reduce the disorder symptoms, and promote and improve the patient's communication skills and ability to cope with the disorder. Psychotherapy has to pay attention to the biological factors involved in schizophrenia and must be aimed at enabling the patient to cope with the disorder and its consequences (acceptance of relapses, self-management, coping with problems). Especially in treatment programmes of longer duration (more than 3 months or more than 10 treatment sessions over 6 months), *cognitive behavioural therapy* (CBT) demonstrated reduction of relapse rates, reduction of psychotic symptoms and improvement of mental state (*Level A*) (NICE 2002). There was evidence that CBT can reduce symptoms in schizophrenic patients up to at least 1-year follow-up. CBT may also improve insight and adherence with drug treatment and have a positive effect on social functioning (NICE 2002).

For *cognitive remediation*, concentrating on improving a particular cognitive deficit, there was only limited evidence for improvements in visual memory, verbal memory and non-verbal reasoning. In a 2-year randomised, controlled study, cognitive enhancement therapy showed superiority with respect to neurocognitive domains, social cognition and social adjustment compared to enriched supportive therapy (Hogarty et al. 2004). Nevertheless, due to limited evidence for the efficacy of cognitive remediation, this approach was not recommended for the routine treatment of people with schizophrenia (NICE 2002).

The evidence for efficacy of *psychoeducation* was discussed controversially. While one systematic meta-analytic review found only limited evidence that psychoeducation, compared to standard care, improved mental state and treatment adherence in follow-ups and showed no effect on relapse rate (NICE 2002), another meta-analysis (Pekkala and Merinder 2004) demonstrated significantly decreased relapse or readmission rates and psychoeducation was supposed to have a positive effect on a

person's well being. Therefore in many guidelines psychoeducational approaches are recommended as useful and should be a part of the treatment programme for people with schizophrenia and related illness (Pekkala and Merinder 2004). Psychoeducation should inform patients and their relatives about the disease and its treatment, promote their understanding of the disease, encourage them to assume responsibility for coping with the disease and support them in disease management (e.g., Bäuml and Pitschel-Walz 2003).

Due to the limited availability of other psychological interventions of proven efficacy, and the preferences of many patients, most guidelines recommend *counselling/supportive psychotherapy* for schizophrenia (DGPPN 1998; NICE 2002, APA 2004). Acceptance and empathic listening contribute to an increasing therapeutic alliance (NICE 2002). Families should be involved and engaged to the greatest possible extent in a collaborative treatment process. Studies showed that family members who have little knowledge of the behavioural manifestations of schizophrenia may be highly critical or overprotective of patients, and these behaviours may increase the likelihood of relapse (e.g., Brown et al. 1972; Bebbington and Kuipers 1994).

Psychodynamic therapy is not recommended in most guidelines for schizophrenic patients due to the lack of randomised controlled studies and the indication is seen only in stable patients due to the potential danger of exacerbating psychosis (e.g., DGPPN 1998; Lehman and Steinwachs 1998; NICE 2002). Psychodynamic therapies should consist of supportive interventions and may then provide individual benefits (Gottdiener and Haslam 2002).

Several clinical trials and some reviews have supported the efficacy of *social skills training* (APA 2004), although a systematic meta-analytic review only found insufficient evidence whether social skills training, compared to all other interventions including the standard, reduce readmission rates or improve quality of life (NICE 2002).

Psychosocial interventions

Family interventions are proposed as adjuncts to drug treatment and demonstrated a decrease in the stress levels within the family and also in the relapse rate (*Level A*) (Pharoah et al. 2004). Additionally, family interventions encouraged compliance with medication and may improve general social impairment and the levels of expressed emotion within the family. Most guidelines recommend family interventions in the treatment of schizophrenia (NICE 2002; APA 2004).

Assertive Community Treatment (ACT), including case management and active treatment interventions by one team using a highly integrated approach, leads to reduced relapse rates and improvement in social functioning (NICE 2002).

In general, *psychiatric rehabilitation* aims to optimise the recovery of individuals with schizophrenia through the use of the full array of biopsychosocial interventions, strengthening the supports and resources available in the community, a collaborative approach with patients and their natural caregivers, and an emphasis on function rather than symptoms. There is an attempt to improve and optimise performance in social, vocational, educational and familial roles in order to achieve the highest quality of life and productivity attainable for individuals with schizophrenia. *Vocational rehabilitation* can include *sheltered workshops* for patients who are not ready for competitive employment with a shortened work day, *job supports*, e.g., in the form of supported employment programmes by providing vocational support on an ongoing basis, and *transitional employment* based in the philosophy of self-help and empowerment (APA 1997, 2004).

Self-help groups give patients and their families tasking and an increasingly active role in the treatment process. Their goals include increasing their influence on treatment planning and implementation, becoming less dependent on professionals, decreasing the stigma associated with mental illness, and working to achieve adequate support for treatment and research in mental illness (APA 1997; DGPPN 1998).

Recommendations

In summary, long-term treatment of patients with schizophrenia has to provide a comprehensive package of treatment options, including pharmacological, psychotherapeutic and psychosocial therapy. Additional components of care, such as integrated care, may contribute to better outcome, reduced social functioning and improved quality of life. In addition to antipsychotic treatment, psychoeducation, family intervention and cognitive behavioural therapy may represent the best approaches to improve psychotic symptoms, impaired social functioning, quality of life and subjective well-being.

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