



TREATMENT GUIDELINES

World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia. Part 3: Update 2015 Management of special circumstances: Depression, Suicidality, substance use disorders and pregnancy and lactation

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TREATMENT GUIDELINES FOR SCHIZOPHRENIA*

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Abstract

These updated guidelines are based on the first edition of the World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia published in the years 2005 and 2006. For this 2015 revision, all available publications pertaining to the biological treatment of schizophrenia were reviewed systematically to allow for an evidence-based update. These guidelines provide evidence-based practice recommendations which are clinically and scientifically relevant. They are intended to be used by all physicians diagnosing and treating patients with schizophrenia. Based on the first version of these guidelines a systematic review, as well as a data extraction from national guidelines have been performed for this update. The identified literature was evaluated with respect to the strength of evidence for its efficacy and subsequently categorised into six levels of evidence (A–F) and five levels of recommendation (1–5). This third part of the updated guidelines covers the management of the following specific treatment circumstances: comorbid depression, suicidality, various comorbid substance use disorders (legal and illegal drugs), and pregnancy and lactation. These guidelines are primarily concerned with the biological treatment (including antipsychotic medication and other pharmacological treatment options) of patients with schizophrenia.

Key words: schizophrenia, comorbid depression, suicidality, comorbid substance use disorder, pregnancy

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General introduction

Despite more than 50 years of pharmacological research there still exists an evidence gap for the treatment of schizophrenia in specific circumstances. Especially for the frequent comorbid conditions of depression and suicidality the knowledge regarding evidence-based treatment options is still sparse. The correct and timely diagnosis of these conditions influences critically the treatment success and thus, physicians involved in the treatment need to pay special attention to these features. The same is true for comorbid substance use disorders since an antipsychotic treatment is likely not to be successful if these are not sufficiently considered. Furthermore, different substances have a great impact on the individual's somatic health which is of particular importance as the main contributors to excess mortality in schizophrenia are somatic disorders (De Hert et al. 2011). Pregnancy and lactation raise the problem that clinical trials evaluating the safety and efficacy of antipsychotics with an adequate study design are very rare. However, case series and systematic reviews of case series at least allow for a satisfying judgment of the available treatment options although they do not fulfil the criteria for high evidence grades. The following sections present updated treatment recommendations for depression, suicidality, substance use disorders, and pregnancy and lactation in adult patients with schizophrenia. As described below, many recommendations had to be based on small randomized controlled trials (RCTs), systematic reviews and observational studies, and expert recommendations take up a specific role in this updated guideline. The limited availability of well-conducted multi-centre randomized trials has to be mentioned as a main limiting factor of our recommendations. Therefore, there is a great need for more research in the field to provide more precise recommendations for the management of these clinically important special treatment circumstances.

Goal and target audience of the WFSBP guidelines

These guidelines are intended for use in clinical practice by all physicians investigating, diagnosing and treating patients with schizophrenia. Therefore, a continuous update of contemporary knowledge of various aspects of schizophrenia with a particular focus on treatment options is provided. The aim of these guidelines is to improve standards of care, to diminish unacceptable variations in the provision and quality of care, and to support physicians in clinical decisions. Although these guidelines favour particular treatments on the basis of the available evidence, the treating physician nevertheless remains responsible

for his assessment and treatment option. These guidelines are primarily concerned with the biological treatment of adults and they address recommendations in this field. The specific aim of these guidelines is to evaluate the role of pharmacological agents and somatic interventions in the treatment and management of schizophrenia, while the role of specific psychological interventions and specific service delivery systems is covered only briefly. The guidelines were developed by the authors and concluded by consensus with the WFSBP Task Force on Schizophrenia, composed of international experts in the field.

Methods of literature research and data extraction

In the development of these guidelines the following guidelines, consensus papers and sources have been considered:

American Psychiatry Association, Practice Guideline for the Treatment of Patients with schizophrenia (APA 1997), American Psychiatric Association, Practice Guideline for the Treatment of Patients with Schizophrenia, Second Edition (Lehman et al. 2004), and APA Guideline Watch: Practice Guideline for the treatment of patients with schizophrenia (Dixon et al. 2009).

The German Association for Psychiatry, Psychotherapy and Psychosomatics (DGPPN). Practice Guidelines Psychiatry and Psychotherapy: Schizophrenia (DGPPN 2006).

National Institute for Clinical Excellence (NICE): Psychosis and schizophrenia in adults: treatment and management (NICE 2014) and other NICE guidelines for separate guidance of special conditions.

Royal Australian and New Zealand College of Psychiatrists: Australian and New Zealand clinical practice guideline for the treatment of schizophrenia (RANZCP 2005).

World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia, Part 1: Acute treatment of schizophrenia (Falkai et al. 2005) and Part 2: Long-term treatment of schizophrenia (Falkai et al. 2006).

The Schizophrenia Patient Outcome Research Team (PORT): Updated Treatment Recommendations 2009 (Kreyenbuhl et al. 2010) and The 2009 Schizophrenia PORT Psychopharmacological Treatment Recommendations and Summary Statements (Buchanan et al. 2010).

The Cochrane Library, Meta-analyses on the efficacy of different drugs and interventions in

schizophrenia (up to September 2014: <http://www.thecochranelibrary.com/details/browseReviews/576837/Schizophrenia-psycho-sis.html>).

The International Psychopharmacology Algorithm Project (IPAP 2014) – The IPAP Schizophrenia Algorithm (2006-03-27): <http://www.ipap.org/>

Reviews, meta-analyses, randomised clinical trials and open label-trials contributing to interventions in schizophrenia patients identified by search in the Medline data base (up to October 2014). For special questions, case reports and case series have been taken into account.

Individual clinical experience by the authors and the members of the WFSBP Task Force on Schizophrenia.

Evidence-based classification of recommendations

Categories of evidence

The evidence-based grading of this update is based on the WFSBP recommendations for grading evidence (Bandelow et al. 2008b) as used recently in the first two parts of these updated guidelines (Hasan et al. 2012, 2013). Daily treatment costs were not taken into consideration due to the variability of medication costs worldwide. In accordance to these first two parts of the guidelines, each treatment recommendation was evaluated and discussed with respect to the strength of evidence for its efficacy, safety, tolerability and feasibility. It must be noted that the strength of recommendation is related to the level of efficacy and tolerability, but not necessarily to the importance of the treatment. Five major categories and three minor categories have been applied to determine the hierarchy of recommendations (related to the described level of evidence) (Hasan et al. 2012, 2013) (see Table I).

Recommendation grades

The recommendation grades are also based on the WFSBP recommendations and adopted from the first revision of the WFSBP Guidelines for the Pharmacological Treatment of Anxiety, Obsessive–Compulsive and Post-Traumatic Stress Disorders (Bandelow et al. 2008a; Hasan et al. 2012, 2013). The aforementioned categories of evidence “are based on efficacy only, without regard to other advantages or disadvantages of the drugs, such as side effects or interactions” (Bandelow et al. 2008a). However, these are important issues for the clinical practice, and therefore, rec-

ommendation grades were also used in these updated guidelines. Thus, the main criteria for evaluation are the safety as well as the tolerability of a given antipsychotic or other drug. For example, the evidence for the efficacy of clozapine in first-episode schizophrenia is good (Category of evidence A), but due to its side-effect profile it is not recommended as a first line treatment for first-episode schizophrenia (Recommendation Grade 2). According to the publication of Bandelow et al. (2008a), “the recommendation grades can be viewed as steps: The first step would be a prescription of a medication with recommendation grade 1. When this treatment fails, all other grade 1 options should be tried first before switching to treatments with recommendation grade 2” (Bandelow et al. 2008a) (see Table I).

Methodological considerations

In contrast to the first two parts of the WFSBP guidelines for the biological treatment of schizophrenia, the database for this third part is limited. Due to the nature of the special circumstances included in this part 3, only few good randomised controlled trials have been conducted so far. However, these special treatment circumstances are of particular importance for patients and caregivers. The recommendations provided below do in fact follow the same evidence-based criteria as the two other parts of these guidelines (Hasan et al. 2012, 2013), but due to the limited number of available publications in the field, systematic reviews and expert opinions have been taken into account specifically.

In this context, the reader should principally note that meta-analyses and systematic reviews have several general limitations. The main problems of meta-analyses and systematic reviews are the comparability of the included studies (e.g., diagnostic differences, different observation periods, different dosages) and the fact that negative results are less frequently published than positive results (publication bias) (Leucht et al. 2009c; Maier et al. 2010). The same can be assumed for systematic reviews. Expert opinions admittedly do not fulfil the highest criteria for evidence-based recommendation, but are rather useful in situations relevant in clinical practice for which only limited data from clinical trials are available.

Depression (see Table II)

Depressive symptoms may occur in all phases of schizophrenia, e.g., first episode, during the early course and after remission, and depression may also contribute to the residual symptoms of schizophrenia. The proportion of patients with schizophrenia

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

| Category of evidence | Description |
|----------------------|---|
| A | Full Evidence From Controlled Studies is based on: two or more double-blind, parallel-group, randomized controlled studies (RCTs) showing superiority to placebo (or in the case of psychotherapy studies, superiority to a “psychological placebo” in a study with adequate blinding) and one or more positive RCTs showing superiority to or equivalent efficacy compared with established comparator treatment in a three-arm study with placebo control or in a well-powered non-inferiority trial (only required if such a standard treatment exists) In the case of existing negative studies (studies showing non-superiority to placebo or inferiority to comparator treatment), these must be outweighed by at least two more positive studies or a meta-analysis of all available studies showing superiority to placebo and non-inferiority to an established comparator treatment. Studies must fulfil established methodological standards. The decision is based on the primary efficacy measure. |
| B | Limited Positive Evidence From Controlled Studies is based on: one or more RCTs showing superiority to placebo (or in the case of psychotherapy studies, superiority to a “psychological placebo”) or a randomized controlled comparison with a standard treatment without placebo control with a sample size sufficient for a non-inferiority trial and no existing negative studies |
| C | Evidence from Uncontrolled Studies or Case Reports/Expert Opinion |
| | C1 Uncontrolled Studies. Evidence is based on: One or more positive naturalistic open studies (with a minimum of five5 evaluable patients) or a comparison with a reference drug with a sample size insufficient for a non-inferiority trial and no existing negative controlled studies |
| | C2 Case Reports. Evidence is based on: one or more positive case reports and no existing negative controlled studies |
| | C3 Evidence is based on the opinion of experts in the field or clinical experience |
| D | Inconsistent Results Positive RCTs are outweighed by an approximately equal number of negative studies |
| E | Negative Evidence The majority of RCTs studies or exploratory studies show non-superiority to placebo (or in the case of psychotherapy studies, superiority to a “psychological placebo”) or inferiority to comparator treatment |
| F | Lack of Evidence Adequate studies proving efficacy or non-efficacy are lacking. |
| Recommendation Grade | Based on |
| 1 | Category A evidence and good risk-benefit ratio |
| 2 | Category A evidence and moderate risk-benefit ratio |
| 3 | Category B evidence |
| 4 | Category C evidence |
| 5 | Category D evidence |

who also manifest depressive symptoms ranges from 7 to 75% (Sands et al. 1999; Siris 2000, 2001; Buckley et al. 2009; Hor et al. 2010; Mosolov et al. 2014). They have to be distinguished from antipsychotic side effects (including medication-induced dysphoria, akinesia and akathisia), and from the primary negative symptoms associated with schizophrenia (Lehman et al. 2004; Falkai et al. 2005; Hasan et al. 2012). Special attention has to be paid to the post-

schizophrenic depression (ICD-10: F20.4) and depressive symptoms after onset of schizophrenia. Furthermore, there are current discussions on whether comorbid depression impacts remission rates in schizophrenia or whether affective symptoms are rather linked to recovery in schizophrenia (Lambert et al. 2010; Mosolov et al. 2014).

The application of self- and clinician-based rating questionnaires can improve the diagnostic

Table II. Recommendations for the management of depressive symptoms in schizophrenia.

| Intervention/Drug/Diagnostic | Category of evidence ^a | Recommendation ^b |
|--|-----------------------------------|-----------------------------|
| Regular assessment of depressive symptoms in schizophrenia | GCP | – |
| CDSS to detect depressive symptoms in schizophrenia | C3 | 4 |
| Wait for the effect of antipsychotics instead of immediately adding an antidepressant | C3 | 4 |
| Use certain antipsychotics in psychosis-associated depression (e.g., quetiapine) | C3 | 4 |
| Use certain antidepressants in post-psychotic depression | C | 4 |
| Use certain antidepressants when the criteria for a major depressive episode are fulfilled | C | 4 |
| Tricyclic antidepressants add-on | C | 4 |
| SSRI add-on | C3 | 4 |
| Other antidepressants add-on | C3 | 4 |
| Closely monitor side-effects when adding antidepressants | GCP | – |
| Closely monitor psychotic symptoms when adding antidepressants | GCP | – |
| Lithium add-on | B | 3 |
| Carbamazepine add-on | E | – |
| Valproate add-on | E | – |
| Lamotrigine | E | – |
| Electroconvulsive Therapy (ECT) | C3 | 4 |
| Repetitive Transcranial Magnetic Stimulation (rTMS) | F | – |

^aCategory of evidence: Category of evidence where A = full evidence from controlled studies (see Table I).

^bSafety rating = recommendation grade derived from categories of evidence and additional aspects of safety, tolerability, and interaction potential. GCP, Good Clinical Practice.

accuracy and should be introduced in unclear cases. Apart from well-established depression rating-scales used in depressive disorders, such as the Beck Depression Scale (BDS), the Hamilton Rating Scale for Depression (HRSD) or the Montgomery–Asberg Depression Rating Scale (MADRS), the Calgary Depression scale for Schizophrenia (CDSS) can be assessed. The CDSS has specifically been developed for schizophrenia, distinguishes between depressive and other symptoms (divergence validity), it shows a high correlation to other depression rating scales (consensus validity) and has a sufficiently predictive validity (Lako et al. 2012). Thus, the use of CDSS to detect depressive symptoms in schizophrenia can be recommended better than the usage of scales primarily developed for major depression (e.g., HRSD) (*Grade of Evidence C3, Level of Recommendation 4*).

Syndromal depression during acute schizophrenia can also occur as part of a schizoaffective disorder. However, a schizoaffective disorder (ICD-10: F25) should only be diagnosed if psychotic and affective symptoms occur at the same time and if both symptom domains have the same intensity. Schizophrenia should be diagnosed if psychotic symptoms had their onset before the depressive symptom, and major depression with psychotic symptoms should

be diagnosed if delusions or hallucinations present are mood-congruent (DGPPN 2006).

Antipsychotics

Depressive symptoms in acute episodes may improve in parallel with psychosis due to antipsychotic treatment (Falkai et al. 2005; Möller 2005) and, thus, the effect of antipsychotics on affective symptoms should be waited for instead of immediately adding an antidepressant (Leucht et al. 2013) (*Grade of Evidence C3, Level of Recommendation 4*). Despite the great clinical impact, data regarding the antidepressive efficacy of antipsychotics after the remission of the acute psychotic episode in patients with schizophrenia is still limited.

For first-generation antipsychotics (FGAs), different studies indicate that these improve depressive symptoms as well as psychotic symptoms in schizophrenia (Abuzzahab et al. 1982; Alfredsson et al. 1984; Dufresne et al. 1993; Krakowski et al. 1997; Mauri et al. 1999). However, this may be dependent on the degree of D2 blockade, and since it is discussed that a high degree of D2 blockade or high FGA doses might also cause depressive symptoms and dysphoria (Van Putten et al. 1978; Pani et al. 2002; Altamura et al. 2003; Falkai et al. 2005).

One should further note that all cited trials are characterised by a small sample size, by a heterogeneity in accessing depressive symptoms and outcome parameters and by the fact that depression was not the primary outcome parameter. One meta-analysis (as detailed below) showed that haloperidol is superior in reducing depression scores in schizophrenia patients compared to placebo (Leucht et al. 2009a). This is not in line with statements from earlier publications which have indicated that FGAs worsen depressive symptoms in schizophrenia patients (e.g., Shanfield et al. 1970; Van Putten et al. 1978; Harrow et al. 1994). However, these findings from acute schizophrenia cannot easily be translated to the long-term course of schizophrenia. Due to the limited amount of studies with an adequate design a conclusive statement is therefore not possible. It can be further discussed that the efficacy of FGAs on depressive symptoms may depend on the degree of D2 blockade (i.e., an inverse U-curve) where a high blockade might actually worsen instead of ameliorate depressive symptoms. Thus, the possibility of an antipsychotic-induced depression needs to be examined thoroughly in patients treated with antipsychotics characterised by a high degree of D2 blockade.

A general superiority of all second-generation antipsychotics (SGAs) compared to FGAs in the reduction of schizophrenia depressive symptoms has been discussed (Möller 2005), but the evidence for this overall superiority is limited. However, as outlined below some SGAs are discussed on the basis of secondary analysis of RCTs, open-label trials and meta-analyses to be superior to FGAs and other SGAs in reducing depressive symptoms in schizophrenia.

One recent secondary analysis of The European First Episode Schizophrenia Trial (EUFEST) could not demonstrate a differential effect of the antipsychotics studied (haloperidol [$n = 103$], amisulpride [$n = 104$], olanzapine [$n = 105$], quetiapine [$n = 104$] and ziprasidone [$n = 82$]) on depressive symptomatology in first-episode schizophrenia patients based on CDSS depression scores (cut-off CDSS > 6 to rate patients as being depressed) (Rybakowski et al. 2012). A secondary analysis from the German Competence Network on Schizophrenia (KNS) conducted on first-episode schizophrenia patients did also not reveal a difference in improving depressive symptoms between treatment with risperidone or haloperidol (Riedel et al. 2012). In the whole sample, the first-episode schizophrenia patients suffering from depression had more suicidal tendencies, less insight into their illness, less social functioning and have achieved remission less often than non-depressed schizophrenia patients (Riedel et al. 2012). A sequential analysis of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study on 1460 multi-episode

schizophrenia patients did not show a difference between the FGA perphenazine and four different SGAs (olanzapine, quetiapine, risperidone and ziprasidone) in the improvement of depressive symptoms (CDSS of ≥ 6 indicative for major depression). However, a small potential difference favouring quetiapine over risperidone in chronic schizophrenia patients with major depressive disorder at baseline was detected (Addington et al. 2011). In addition, one RCT showed that quetiapine treatment resulted in a greater reduction of depression scores compared to haloperidol in 269 schizophrenia patients (Emsley et al. 2003). A randomised controlled double-blind trial with 1996 schizophrenia patients showed that both, olanzapine and haloperidol, reduced depressive symptoms (BPRS anxiety-depression cluster and MADRS), but that this improvement was greater in the olanzapine group. One pragmatic rater-blind RCT conducted on 226 schizophrenia patients to compare olanzapine, quetiapine, risperidone and ziprasidone could not display a clinically relevant difference in anti-depressive effectiveness among the study drugs in patients acutely admitted to hospital for symptoms of psychosis (Kjelby et al. 2011).

One small open-label trial with limited sample size ($n = 39$) showed that quetiapine is effective for the treatment of depressive symptoms in patients with schizophrenia (Lee et al. 2009). One data from open-label extension phases of three randomized clinical trials of quetiapine in patients with schizophrenia with a total sample size of 415 investigated the Factor I score of the Brief Psychiatric Rating Scale after 6 and 156 weeks, respectively, showed that quetiapine is effective for the treatment of anxiety and depressive symptoms in schizophrenia and that this effect is maintained for the period following the acute phase of the illness (Kasper 2004).

One randomised open-label trial showed that the switch from risperidone to amisulpride ($n = 42$) improved depressive symptoms compared to the continuation of risperidone treatment ($n = 45$) in schizophrenia patients with comorbid depression (Kim et al. 2007). A randomised 8-week double-blind comparison of amisulpride and olanzapine of 85 schizophrenia patients with comorbid depression showed that both these antipsychotics were effective in improving depressive symptoms with no differences between the study drugs (Vanelle et al. 2006). In a 24-week RCT schizophrenia and schizoaffective patients with prominent depressive symptoms were either treated with olanzapine ($n = 202$) or with ziprasidone ($n = 192$). Patients randomized to olanzapine had a greater and more sustained participation in treatment with greater improvement in depressive symptoms and global functioning (Kinon et al. 2006). However, olanzapine-treated patients had a

greater increase in metabolic parameters. A comparison of olanzapine ($N=40$) and risperidone ($N=36$) in an 8-week, randomized, double-blind, parallel-group study in schizophrenia patients suffering from post-psychotic depression showed that both drugs significantly decreased MADRS scores (Dollfus et al. 2005). One double-blind RCT used the PANSS depression cluster and showed that olanzapine treatment was associated with a higher categorical rate of improvement on the PANSS depression cluster compared to a treatment with risperidone. Furthermore, patients receiving risperidone and having experienced a great degree of acute mood change were more likely to relapse than those patients who experienced less mood improvements (3.58 times) and those who received olanzapine with similar mood improvement (8.55 times) (Tollefson et al. 1999). Another subanalysis of schizophrenia patients from a randomized, open-label, parallel-group, flexible-dose study (Di Fiorino et al. 2014) compared the efficacy of quetiapine XR (ITT $n=59$) and risperidone (ITT $n=51$) with regard to change in CDSS scores from baseline to week 12 (Kasper et al. 2015). The analysis showed that quetiapine XR is not only non-inferior but also numerically superior to risperidone in reducing depressive symptoms during the study period (Kasper et al. 2015).

One meta-analysis conducted on the basis of 150 double-blind, mostly short-term studies with 21,533 participants to compare the efficacy between SGAs and FGAs showed that the SGAs amisulpride, aripiprazole, clozapine, olanzapine and quetiapine were significantly superior to FGAs in improving depressive symptoms in schizophrenia patients (effect sizes 0.1–0.5), whereas this effect could not be shown for risperidone and other SGAs (Leucht et al. 2009b). Another meta-analysis from the same group based on 38 RCTs with 7323 participants to compare the efficacy of SGAs (and haloperidol) to placebo showed on the basis of a subgroup analysis with limited data (14 studies) that SGAs as a group are superior to placebo in reducing depressive symptoms (Leucht et al. 2009a). Furthermore, amisulpride, olanzapine, ziprasidone, zotepine and haloperidol (see above) were statistically found significantly superior to placebo (Leucht et al. 2009a). One systematic Cochrane review investigated the effects of SGAs for patients with both schizophrenia and depression but was unable to draw definitive conclusions (Furtado et al. 2008). These analyses revealed that patients treated with sulpiride had a lower depression score than those treated with chlorpromazine, but showed no differences between quetiapine and haloperidol. In this context, small to moderate doses of substituted benzamides have been discussed to be effective in the treatment of comorbid depression (Pani et al.

2002), but further studies are needed to give specific evidence-based recommendations. Furthermore, the comparison of clozapine with any other antipsychotic plus antidepressant agent or placebo showed that patients receiving clozapine consistently scored better on Hamilton depression scores (Furtado et al. 2008). This overview illustrates clearly that most studies did not target the improvement of depressive symptoms in schizophrenia as primary outcome. Thus, these trials have not been primarily designed to investigate the efficacy of antipsychotics on depressive symptoms in schizophrenia and the inclusion criteria usually have not had a certain depression score as cut-off for the participation in the respective trial. The result is that many patients in these trial only have modest depression scores – this fact might not be sensitive enough to prove an efficacy of intervention.

For some of the aforementioned antipsychotics (mainly quetiapine), the efficacy in major depression and in bipolar depression has been shown (e.g., Cruz et al. 2010; Komossa et al. 2010; De Fruyt et al. 2012). For example the high quality German Practice Guidelines Psychiatry and Psychotherapy recommend quetiapine as monotherapy for bipolar depression with sufficient evidence (DGBS/DGPPN 2014). The translation of the efficacy from major depression to schizophrenia is in itself somewhat doubtful, but it appears likely that compounds with a high affinity for the D2 site are less effective for the treatment of comorbid depression (or could even worsen symptoms by higher doses) and that a blockade of serotonin 5-HT_{2A} receptors may have an effect in itself as such. Finally, as a continuation of FGA treatment compared to a drug withdrawal reduces the onset of depressive symptoms, a similar effect can be assumed for SGAs (Wistedt et al. 1983; DGPPN 2006).

Antidepressants

As outlined above, depressive symptoms occurring during an acute schizophrenia should not be automatically treated with an antidepressant (Leucht et al. 2013). In the previous versions of these guidelines we stated that due to potential worsening of psychosis by antidepressive agents during the acute phase, antidepressants are advocated primarily as adjunctive treatment in the stable phase of schizophrenia (Falkai et al. 2006). This is in line with statements from other guidelines (Lehman et al. 2004; DGPPN 2006), but the overall risk to induce psychosis can presently be considered to be small (Leucht et al. 2013). Most guidelines recommend the administration of antidepressants as add-on treatment with a limited evidence-level when

- (1) the patient's symptoms meet the syndromal criteria for a major depressive disorder;
- (2) the symptoms are severe and thus clinically relevant;
- (3) when they cause significant distress; or
- (4) when they interfere with functioning (DGPPN 2006; Falkai et al. 2005; Lehman et al. 2004).

The PORT guidelines (Buchanan et al. 2010; Kreyenbuhl et al. 2010) are more rigorous regarding the use of antidepressants for this indication in schizophrenia. They state that due to the lack of data for new antidepressants as well as for the combination with SGAs, the level of evidence is currently insufficient to support a recommendation for the use of adjunctive antidepressants for the treatment of depression in schizophrenia (Buchanan et al. 2010). However, especially in cases of post-psychotic depression fulfilling the ICD-10 criteria the introduction of an antidepressant should be discussed, dependent on the clinical need of a given patient (*Category of Evidence C3, Level of Recommendation 4*).

Add-on studies using modern antidepressants and focusing on relevant depressive symptoms in schizophrenia are still sparse, so that most recommendations can only be given for tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs). Furthermore, most studies have been conducted adding antidepressants to an ongoing treatment with an FGA only, so that the knowledge regarding the add-on antidepressant treatment to an ongoing SGA treatment is still sparse.

The evaluation of antidepressants for the treatment of schizophrenia negative symptoms is presented in the first part of this updated guideline (Hasan et al. 2012).

Selective serotonin reuptake inhibitors (SSRIs)

For SSRIs, one double-blind, placebo-controlled study conducted on only 26 patients with chronic and stable schizophrenia revealed that sertraline is superior to placebo in improving depressive symptoms in terms of BDI and HDRS values (Mulholland et al. 2003). Another small RCT ($N=40$) comparing sertraline and imipramine in post-psychotic depression revealed comparable efficacy, but more rapid onset with sertraline (Kirli et al. 1998). Another RCT tested the efficacy of a citalopram ($N=104$) augmentation compared to placebo ($N=94$) for suicidal ideation in 198 schizophrenia and schizoaffective patients. The results showed that treatment-emergent suicidal ideation was no more common with citalopram than placebo and that in patients with baseline suicidal ideation, citalopram

actually reduced suicidal ideation, especially in those patients with depressive symptoms who responded to treatment (Zisook et al. 2010). In general, SSRIs have been discussed to be useful in the treatment of depression in schizophrenia (Siris 2000, 2001). However, a further double-blind, placebo-controlled study conducted on 48 patients meeting DSM-IV criteria for both schizophrenia in remission and for a major depressive episode could not show a superiority of sertraline compared to placebo in improving depressive symptoms and in both study groups between 40 and 50% of patients showed a 50% reduction in depression score (Addington et al. 2002). Thus, the high placebo response in this trial might account for the negative finding.

Other modern antidepressants

The selective serotonin and noradrenalin reuptake inhibitor (SNRI) venlafaxine added to an ongoing antipsychotic treatment was tested in one small open-label trial. Nineteen schizophrenia patients suffering from a major depressive episode after a 4-week observation period were treated with add-on venlafaxine and 14 patients showed an improvement in HDRS scores and an exacerbation of psychotic symptoms was not reported by the authors (Mazeh et al. 2004). A double-blind randomized controlled trial conducted on 41 schizophrenia patients compared mirtazapine with placebo when added to an ongoing FGA treatment and showed a superiority of mirtazapine in improving depressive symptoms according to CDSS scores (Terevnikov et al. 2011). Case reports and systematic reviews indicate that bupropion is effective in the treatment of depression in schizophrenia with no increased risk for psychotic exacerbation. However, placebo-controlled trials are missing (Englisch et al. 2010, 2013).

Tricyclic antidepressants (TCAs)

Tricyclic antidepressants (TCAs) were primarily examined in the treatment of post-psychotic depression long before the introduction of the first SSRI (Plasky 1991; Siris 2000). A systematic review identified 11 studies with each sample smaller than 30 subjects published between 1983 and 1995 which tested the efficacy of various antidepressants (TCA: imipramine, desipramine, amitriptyline, nortriptyline, desimipramine; other: bupropion, viloxazine, trazodone, as add-on to an ongoing antipsychotic treatment (all FGAs)) for the treatment of depression in schizophrenia. This analysis provided evidence for a modest benefit of antidepressants for this indication (Whitehead et al. 2003). One controlled

trial with limited sample size ($n = 24$) not analysed in the previously mentioned systematic review showed that the add on of imipramine in schizophrenia patients suffering from secondary depression or negative symptoms is superior to a placebo treatment (Siris et al. 1994). However, an exacerbation of psychotic symptoms with low likelihood following an add-on treatment with TCAs (e.g., in schizophrenia or delusional depression) has been reported in earlier reports (Nelson et al. 1979; Prusoff et al. 1979; Plasky 1991).

Summary recommendations

- Patients with schizophrenia should regularly be assessed regarding depressive symptoms by a clinical interview (*Good Clinical Practice*).
- The CDSS (if not available: MADRS or HRDS) should be used primarily to specifically detect depressive symptoms in schizophrenia patients (*Grade of Evidence C, Level of Recommendation 4*).
- Certain antipsychotics have the potential to improve depressive symptoms in patients with acute schizophrenia (*Grade of Evidence C, Level of Recommendation 4*). In the SGA group, risperidone seems to be inferior to other SGAs (amisulpride, aripiprazole, clozapine, olanzapine and quetiapine) for this indication (*Grade of Evidence C3, Level of Recommendation 4*) and quetiapine seems to be consistently effective in reducing depressive symptoms in schizophrenia (*Grade of Evidence C3, Level of Recommendation 4*). FGAs should not be primarily used for the treatment of depressive symptoms in schizophrenia (*Grade of Evidence C3, Level of Recommendation 4*).
- There are almost no new data regarding the application of antidepressants for the treatment of depressive symptoms in schizophrenia. However, there is limited evidence that TCAs and other antidepressants (e.g., SSRIs, dual reuptake inhibitors, others) are useful in the treatment of depressive symptoms which fulfil the criteria for a major depression in schizophrenia patients. Due to the limited evidence available the evidence grading was reduced from B to C3 (*Grade of Evidence C3, Level of Recommendation 4*).
- When introducing antidepressants, potential pharmacokinetic interactions with certain antipsychotics need to be considered (*Grade of Evidence C3, Level of Recommendation 4*). For example, the SSRIs (such as fluoxetine,

paroxetine, and fluvoxamine) are inhibitors of cytochrome P450 enzymes and therefore increase antipsychotic plasma levels. Similarly, the blood levels of some antidepressants may be elevated by the concomitant administration of antipsychotic medications (Falkai et al. 2005).

- An increase of, e.g., agitation or psychotic symptoms needs to be monitored but this risk should be considered as moderate (*Good Clinical Practice*). However, in cases of acute schizophrenia a particular caution is recommended.
- Side-effects like QTc-prolongation, agranulocytosis, haematological changes or the lowering of epileptic threshold with induction of epileptic seizures (e.g. bupropion) can occur or increase when combining certain antidepressants with antipsychotics and need to be monitored (*Good Clinical Practice*).
- There is a great need for multi-centric trials to investigate the efficacy of antidepressive treatment in schizophrenia-associated depression and despite the great incidence and impact of this condition such trials are still not available.

Mood stabilisers

The efficacy of mood stabilisers as augmentation strategy in schizophrenia has been extensively described in the first part of this updated guideline (Hasan et al. 2012). Lithium is recommended in different guidelines for the treatment of affective symptoms in schizophrenia (Lehman et al. 2004; DGPPN 2006) with good to limited evidence and this recommendation can also be extracted from one meta analysis (Leucht et al. 2004). The add-on treatment with lithium underwent a critical discussion during the revision process and as the overall effects of lithium on depressive symptoms in schizophrenia have not been shown in all studies (Lehman et al. 2004), the group decided to change the evidence grade from A (Falkai et al. 2005) to B (*Grade of Evidence B, Level of Recommendation 3*). Furthermore, lithium needs a mandatory monitoring of its blood level and has a small therapeutic range. These factors have to be taken into consideration when introducing lithium in patients with schizophrenia.

Valproate and carbamazepine seem also to have a beneficial effect on depressive symptoms (Falkai et al. 2005; DGPPN 2006), but are also discussed to worsen schizophrenia symptoms or increase side-effects (e.g., through lowering antipsychotic plasma levels by drug interactions) (Hasan et al. 2012).

Thus, the usage of these drugs for the treatment of depressive symptoms in schizophrenia cannot be recommended with sufficient evidence. For lamotrigine, a mood stabiliser frequently used in major depression, no beneficial effect on depressive symptoms in schizophrenia could be detected (CDSS as secondary outcome) (Glick et al. 2009; Vayisoglu et al. 2013) and no trial primarily targeting these symptoms in schizophrenia is available.

Electroconvulsive therapy (ECT)

The APA guidelines for the treatment of schizophrenia recommend ECT for patients with comorbid depression and/or suicidal ideation in situations where a rapid therapeutic response is needed (Lehman et al. 2004). Since the publication of our last guidelines (Falkai et al. 2005, 2006; Hasan et al. 2012, 2013), one systematic review for ECT in schizophrenia has been published (Pompili et al. 2013). The authors reviewed 31 trials and provided only inconsistent evidence for the use of ECT in the treatment of depressive and/or suicidal behaviour in schizophrenia (Pompili et al. 2013). Thus, ECT can only be recommended in certain cases with severe depression and/or suicidal behaviour with limited evidence (*Grade of Evidence C3, Level of Recommendation 4*).

Repetitive transcranial magnetic stimulation (rTMS)

rTMS is recommended for the treatment of major depression (Lefaucheur et al. 2014), but there is currently no sufficient evidence to recommend rTMS for the treatment of depressive symptoms in schizophrenia. One poster of a small open-label trial indicated the efficacy of rTMS applied to the left dorsolateral prefrontal cortex (DLPFC) for the treatment of marked depression (CDSS score > 6) in schizophrenia (Maslenikov et al. 2008). However, one randomized and sham-controlled multicentric

trial included 157 schizophrenia patients with predominant negative symptoms and could not find a superior beneficial effect of 10-Hz rTMS applied for 3 weeks to the left DLPFC on depressive symptoms (CDSS secondary outcome; mean CDSS > 5) in schizophrenia immediately after intervention (Wobrock et al. 2014).

Suicidality (see Table III)

Approximately 5 to 15% of patients with schizophrenia will commit suicide, and the rate of at least one suicide attempt is 2 to 5 times higher than in the normal population (Caldwell et al. 1990; Siris 2001; Meltzer 2005; Pompili et al. 2011). In the first analysis of the absolute risk of suicide in a total national cohort of individuals followed up from the first psychiatric contact, Nordentoft et al. (2011) reported that schizophrenia was the first psychiatric disorder responsible of completed suicide in women (cumulative incidence of 4.91%) and the third in men (cumulative incidence of 6.55%). One meta-analysis on 61 studies with a sample size of 48,176 reported a cumulative lifetime suicide risk of 4.9% in schizophrenia patients with an emphasis on the early disease stages (Palmer et al. 2005). Apart from somatic comorbidities (e.g., metabolic syndrome and cardiovascular diseases) (Laursen et al. 2011), suicide is one of the leading causes of excess mortality in schizophrenia patients (Brown 1997; Meltzer 2002b). Cohort studies and long-term follow-up studies have shown that approximately 10% of patients with first-episode schizophrenia attempted suicide within one year, whereas hallucinations, previous suicidal behaviour and the time period after the early onset of the disease represented the greatest risk factors (Nordentoft et al. 2002; Palmer et al. 2005; Bertelsen et al. 2007; Shrivastava et al. 2010). A nested case-control study revealed that the first year of treatment (which can be considered early in the course of the

Table III. Recommendations for the management of suicidality in schizophrenia.

| Intervention/Drug/Diagnostic | Category of evidence ^a | Recommendation ^b |
|---|-----------------------------------|-----------------------------|
| Regular assessment of suicidality in schizophrenia | GCP | – |
| Regular assessment of motor side effects | C3 | 4 |
| Consider hospitalisation | C3 | 4 |
| Antipsychotics as a group reduce suicidal behaviour | C | 4 |
| Clozapine for suicidality in schizophrenia | B | 3 |
| Lithium add-on in patients with mood symptoms | C3 | 4 |
| Antidepressants add-on in patients with mood symptoms | C3 | 4 |

^aCategory of evidence: Category of evidence where A = full evidence from controlled studies (see Table I).

^bSafety rating = recommendation grade derived from categories of evidence and additional aspects of safety, tolerability, and interaction potential. GCP, Good Clinical Practice.

illness) is associated with a 60% increased risk for committing suicide compared to other disease states (Nordentoft et al. 2004; Pompili et al. 2011). A retrospective analysis conducted on the data of 696 patients indicates that the first month of treatment is associated with the highest risk for suicide, but that the risk decreases over the following 6 months and after that decline more slightly (Fedyszyn et al. 2010). However, it should be noted that the rates of suicides and suicide attempts show a broad variance across studies (Pompili et al. 2011).

Demographically associated with suicidality in schizophrenia are factors such as young age (< 20 years), male gender, a high socioeconomic family background, a high premorbid IQ and better cognitive functioning, high expectations, being unmarried, the lack of social support, the awareness of the symptoms, a recent discharge from hospital, and more than five hospital admissions (Heila et al. 1997; Lehman et al. 2004; Falkai et al. 2005; Bakst et al. 2010). Factors associated with an increased risk of suicide are reduced self-esteem, stigmatization, recent experience of loss or stress, hopelessness, isolation as well as treatment non-adherence (e.g., De Hert et al. 2001; Siris 2001; Pompili et al. 2011).

The most common clinical correlates of suicidality in schizophrenia are depressive symptoms, substance dependency (including tobacco dependency), severity of psychotic symptoms and thought disorders, early disease stages, insomnia, agitation and motor restlessness (e.g., Birchwood et al. 2000; Siris 2001; Nordentoft et al. 2002; Altamura et al. 2003; Palmer et al. 2005; Bertelsen et al. 2007; Pompili et al. 2009; Bakst et al. 2010; Barrett et al. 2010; Crocq et al. 2010; Schennach-Wolff et al. 2010; Shrivastava et al. 2010). Furthermore, transcultural differences play a significant role in the evaluation of suicidality in schizophrenia patients (Altamura et al. 2007). Suicide attempts by patients with schizophrenia are more frequently fatal, which indicates that more lethal methods are used (Beautrais 2001; Falkai et al. 2005). One of the most important predictors of suicide in schizophrenia is a case history and its recent suicide attempts (Pompili et al. 2007; Reutfors et al. 2009; Bakst et al. 2010). Suicidal ideations or threats should be judged in the context of a patient's history as provided by the patient, by relatives and the current therapist, if available (APA 1997; Lehman et al. 2004; Falkai et al. 2005). There should be a close monitoring of vulnerable patients during times of personal crises, significant environmental changes or heightened distress or depression during the course of illness. The frequency of outpatient visits may need to be increased during vulnerable periods, especially after a recent discharge from hospital (APA 1997; Lehman et al. 2004; Falkai et al. 2005).

Pharmacological treatment of suicidality

Open and RCTs as well as register studies indicate that antipsychotic treatment with FGAs and SGAs including the respective depot formulations is effective in reducing suicidality in schizophrenia patients (Wilkinson et al. 1984; Keck et al. 2000; Khan et al. 2001; Barak et al. 2004; Haukka et al. 2008; Tiihonen et al. 2009). However, this statement is still subject to controversial discussions (Tondo et al. 2001) (*Category of Evidence C3, Recommendation Grade 4*). A clear clinical relevant difference in the efficacy between FGAs and SGAs for this indication has not been shown. One cohort study with a 4-year observation period revealed an increased risk for all-cause death and suicide in thioxanthenes users compared to those patients treated with phenothiazines, butyrophenones or benzamides (Montout et al. 2002). Furthermore, a negative attitude towards treatment and a poor adherence to medication have been identified as risk factors for suicide in schizophrenia (De Hert et al. 2001).

At the same time, physicians and other caregivers should be aware that severe antipsychotic side-effects can also result in suicidal ideation and behaviour, probably due to the increased motor activity (Mamo 2007). Based on a review and early data from small studies and case series (Mamo 2007) motor side-effects, especially akathisia (Shear et al. 1983; Drake et al. 1985; Kerwin 2003; Lehman et al. 2004) have been linked to an increased risk for suicidal behaviour. Thus, special attention should be paid to motor side-effects, and in cases of suicidal behaviour antipsychotics with reduced risk for these side-effects should be used (*Category of Evidence C3, Level of Recommendation 4*). References regarding the risk of motor side-effects associated with FGA and SGA treatment can be found in the first part of these updated guidelines (Hasan et al. 2012). One 5-year case-controlled retrospective study showed that olanzapine and risperidone may have a protective potential regarding suicidality in schizophrenia and that risperidone had a higher effect-size without reaching statistical significance (Barak et al. 2004). One analysis of The Sertindole Cohort Prospective (SCoP) study compared schizophrenia patients who were randomly assigned to either sertindole (4905 patients) or risperidone (4904 patients) in a parallel-group open-label design. The total exposure was 6978 and 7975 patient-years in the sertindole and risperidone groups, respectively. The suicide mortality was low in this population (0.21 [sertindole] and 0.28 [risperidone] per 100 patient-years of treatment), but sertindole was statistically superior (Crocq et al. 2010).

A 1995 study showed that clozapine treatment reduced suicidality in antipsychotic schizophrenia

patients (85% decrease rate) (Meltzer et al. 1995). The results of a 2-year randomized, open label, rater-blinded trial with 980 schizophrenia and schizoaffective patients (International Suicide Prevention Trial, the InterSeP trial), with the study endpoints suicide attempt or hospitalization to prevent a suicide attempt, showed that the treatment with clozapine as compared to olanzapine was associated with a reduced risk of attempt suicide, a reduced need for hospitalization and for rescue interventions to prevent suicide compared to treatment with olanzapine (Meltzer et al. 2003). However, few of these high-risk patients died from suicide (five clozapine and three olanzapine patients) and the study could not demonstrate a specific preventive effect of clozapine on completed suicide.

Furthermore, additional analyses of this study indicated that olanzapine and clozapine improve the awareness of disorder and that this increase in awareness was associated with a decreased risk of suicide events (Bourgeois et al. 2004). Another secondary analysis of this study aimed to investigate the application of concomitant psychotropic medications (other antipsychotics, antidepressants, sedatives/anxiolytics, mood stabilizers) and showed that patients reaching the study endpoint had a higher use of concomitant medication when assigned to the olanzapine group (Glick et al. 2004). Moreover, one retrospective evaluation of 94 inpatients in a mirror design also showed that clozapine reduces the frequency of suicidal behaviour and suicidal events (Modestin et al. 2005). In addition, a linkage-analysis between a national registry of clozapine recipients with the US National Death Index and Social Security Administration Death Master Files indicated that clozapine reduces the mortality in severe schizophrenia by decreasing suicide rates (Walker et al. 1997).

One meta-analysis and one review supported the notion that clozapine decreases suicidal risk (Wagstaff et al. 2003; Hennen et al. 2005), but one retrospective analysis from the Department of Veterans Affairs (Centralized VA databases and a national death registry) could not confirm this superiority of clozapine (Sernyak et al. 2001), although this had been criticised for methodological reasons (design of control group, possibility of a nearly significant effect of clozapine treatment (Ertugrul 2002; Meltzer 2002a, Meltzer 2005)). The statement that clozapine reduces suicidality in schizophrenia patients can be found in various national and international guidelines and consensus papers (Lehman et al. 2004; RANZCP 2005; DGPPN 2006; Moore et al. 2007; Buchanan et al. 2010; Wasserman et al. 2012). Clozapine has been approved by the FDA for the indication to reduce the risk of committing suicide in schizophrenia patients at high risk for suicide (Melt-

zer 2005). These various considerations seem to corroborate the assumption that clozapine should be introduced for schizophrenia patients suffering from persistent suicidal thoughts or suicidal behaviour and thus are at high risk for suicide (*Category of Evidence B, Level of Recommendation 3*).

Another pharmacological option for suicidality in schizophrenia is lithium. Lithium has been shown to improve affective symptoms in schizophrenia patients (see part 1 of the updated WFSBP guidelines (Leucht et al. 2004; Hasan et al. 2012)) and the APA guidelines have recommend the prescription of conservative quantities for patients at increased risk for suicidal behaviours (Lehman et al. 2004). However, a direct evidence for the efficacy of lithium to improve suicidality in schizophrenia from RCTs is lacking.

Summary recommendations

- Suicide risk must be actively monitored and responded to (Lehman et al. 2004; RANZCP 2005) in all phases of the illness (*Good Clinical Practice*).
- Comorbid depression needs to be identified as early as possible and a treatment should be initiated (*Category of Evidence C3, Level of Recommendation 4*).
- For patients at high risk for suicide, hospitalization should be considered and suicide precautions should be instituted (Lehman et al. 2004) (*Category of Evidence C3, Level of Recommendation 4*).
- The discharge from hospital represents a critical phase for suicidality. Thus, the frequency of outpatient visits should be higher after hospital discharge and outpatient visits should be adapted to the level of individual stress (Lehman et al. 2004) (*Category of Evidence C3, Level of Recommendation 4*).
- It is important to maximize the somatic treatment of psychosis and depression and address patients' suicidality directly with an empathic and supportive approach (Lehman et al. 2004) (*Category of Evidence C3, Level of Recommendation 4*).
- Both, FGAs and SGAs have been shown to be effective in reducing suicidality (*Category of Evidence C, Level of Recommendation 4*), whereas some inconsistency across studies needs to be considered. Special caution should be given to motor-side-effects and akathisia which need active monitoring.
- The best evidence to reduced suicidal ideation and suicide rate is available for clozapine. Clozapine should be considered if there

is a significant and continuously increased risk of suicide (*Category of Evidence B, Level of Recommendation 3*).

- In patients with mood symptoms, lithium can be introduced for the treatment of suicidality (*Category of Evidence C3, Level of Recommendation 4*) (see above).
- In patients with depressive symptoms, antidepressants can be introduced for the treatment of suicidality combined with a very close monitoring of suicidal intentions, thus taking care of the possible elevation of the inner drive before reducing depressive mood (*Category of Evidence C3, Level of Recommendation 4*) (see above).

Substance use disorders (see Table IV)

Alcohol and illegal substance abuse and dependency

Substance and alcohol abuse in individuals with schizophrenia is very common and is the most prevalent comorbid psychiatric condition associated with schizophrenia. The reported prevalence rates of substance abuse and dependency in schizophrenia range

from 15 to 65% depending on the substance type (Kovaszny et al. 1997; Buckley et al. 2009). One analysis provided by the Genomic Psychiatry Cohort consisting of 9142 patients with severe psychotic illness (schizophrenia, bipolar disorder with psychotic features and schizoaffective disorder) and 10,195 control individuals, showed that severe psychotic disorders have increased risks for smoking, heavy alcohol consumption, heavy cannabis use and recreational drug use (Hartz et al. 2014). The following section has been in parts adopted from the last version of this guideline (Falkai et al. 2005) and updated with new evidence where necessary.

Comorbid substance use disorder (SUD) has been associated with more frequent and longer periods of hospitalization and other negative outcomes, including higher relapse rate, even in first-episode patients, higher non-compliance, elevated rates of motor side-effects in general and during antipsychotic treatment, unemployment, homelessness, violence, incarceration, suicide and HIV infection (Mueser et al. 1990; Soyka et al. 1993; Drake et al. 2001; Hunt et al. 2002; Lacro et al. 2002; Wobrock et al. 2008). Apart from legal substances such as tobacco and alcohol, cannabis is the most abused

Table IV. Recommendations for the management of comorbid substance use disorders in schizophrenia.

| Intervention/Drug/Diagnostic | Category of evidence ^a | Recommendation ^b |
|--|-----------------------------------|-----------------------------|
| Detailed assessment of substance use disorder | GCP | – |
| Specific psychosocial interventions for dual diagnosis of schizophrenia and substance use disorder ¹ | C3 | 4 |
| Specific psychosocial interventions with motivational and behavioural components for dual diagnosis of schizophrenia and alcohol dependency ² | B | 3 |
| Specific psychosocial interventions for schizophrenia patients with comorbid tobacco dependency | C3 | 4 |
| <i>Alcohol</i> | | |
| Clozapine for the dual diagnosis of schizophrenia and alcohol dependency | B | 3 |
| Antipsychotics as a group for the dual diagnosis of schizophrenia and alcohol dependency | C3 | 4 |
| Acamprosate for patients with a dual diagnosis of schizophrenia and alcohol dependency | C2 | 4 |
| Naltrexone for patients with a dual diagnosis of schizophrenia and alcohol dependency | B | 3 |
| <i>Others</i> | | |
| Clozapine for the dual diagnosis of schizophrenia and other substance use disorders | C3 | 4 |
| Antipsychotics as a group for the dual diagnosis of schizophrenia and cocaine dependency | B | 3 |
| Long-acting injectable antipsychotics for the dual diagnosis of schizophrenia and substance abuse disorder due to the elevated non-compliance | C3 | 4 |
| <i>Tobacco</i> | | |
| Initiate smoking cessation only in patients with stable psychopathology | GCP | – |
| Nicotine replacement therapy | B | 3 |
| Bupropione add-on | B | 3 |
| Varenicline add-on | D | 5 |

^aCategory of evidence: Category of evidence where A = full evidence from controlled studies (see Table I).

^bSafety rating = recommendation grade derived from categories of evidence and additional aspects of safety, tolerability, and interaction potential. GCP, Good Clinical Practice.

¹The overall recommendation across guidelines for such specific interventions is positive. However, recent negative studies and differences in the intervention need to be taken into account.

²The efficacy for psychosocial interventions in patients with a dual diagnosis of schizophrenia and alcohol dependency is more consistent compared to other substance use disorders

illicit drug in schizophrenia and has been discussed as an important risk factor for developing schizophrenia (e.g., Martinotti et al. 2012; Radhakrishnan et al. 2014).

The presence of substance abuse or dependence is often not recognized and systematically assessed, especially if such a patient is seen during an acute psychotic episode. Because self-report may be unreliable, corroborating evidence from all sources including laboratory tests (e.g. liver enzymes, carbohydrate-deficient transferrin, blood cell count and mean corpuscular/cell volume of erythrocytes) and drug screening (urine and blood) should be sought. The effects of abused substances on schizophrenia symptoms vary, making the differentiation of substance abuse-related symptoms from those related to functional psychosis difficult (Lehman et al. 2004). In clinical practice, information from family members or friends can help identify comorbid substance abuse and the application of specific questionnaires (e.g., Alcohol Use Disorders Identification Test (AUDIT) or Dartmouth Assessment of Lifestyle Instrument) might also provide important information (Lehman et al. 2004). The abused substances may lead to increased hallucinations, paranoid symptoms or anxiety in patients with pre-existing schizophrenia (e.g., Dixon et al. 1991). In some cases it may be extremely difficult to distinguish schizophrenia from drug-induced psychosis and only the longitudinal observation under abstinence conditions may allow clarification.

Psychosocial treatment

This has been partly adopted from the last version of these WFSBP guidelines (Falkai et al. 2005) and updated where necessary. The key issue in providing treatment for this population is to develop a dual disorder approach that integrates treatment of substance abuse and of schizophrenia (Ridgely et al. 1996; Drake et al. 2000, 2001; Murthy et al. 2012). As has been described in detail (Falkai et al. 2005), different psychosocial treatment programmes provide this integration by interdisciplinary teams with expertise in the treatment of schizophrenia and substance abuse. This form of treatment features:

- assertive outreach, case management, family interventions, housing, rehabilitation therapy and pharmacotherapy;
- a stepwise motivational approach for patients who are oblivious of the need for treatment of substance use disorders;
- behavioural interventions for those trying to attain or maintain abstinence; and
- elements of cognitive behavioural therapy.

There is sufficient evidence showing that combined treatment programmes with motivational elements, psychoeducation and cognitive-behavioural approaches which avoid direct confrontation can be effective in reducing substance abuse and in decreasing the frequency and severity of psychotic decompensations (Addington et al. 1998; Herman et al. 2000; Barrowclough et al. 2001; Drake et al. 2001; Hellerstein et al. 2001; Baker et al. 2002). Additional evidence is provided from a recent open, but non-randomized study comparing an integrated treatment programme ($N=85$) with treatment as usual ($N=35$) in patients suffering from schizophrenia with comorbid SUD. The integrated treatment programme was adopted from Drake et al. (2004) and analyses revealed that this intervention improved different symptom domains of schizophrenia as well as the amount of drug use at the end of 3 months, and that most improvements could be maintained for 12 months (Morrens et al. 2011).

However, recent large-scale trials question these general recommendations. A well-conducted trial that followed the CONSORT guidelines for non-pharmacological trials compared the efficacy of a specific intervention ($N=164$; 26 therapy sessions in 12 months, motivational interviewing, CBT elements) (Barrowclough et al. 2009) with standard care ($N=163$) in patients with schizophrenia or schizophreniform/schizoaffective disorder and comorbid substance abuse (Barrowclough et al. 2010). In this trial, the primary outcome (death from any cause or admission to hospital in the 12 months after completion of therapy) did not differ between both groups. Secondary outcomes like perceived consequences of substance abuse and clinical outcomes also did not differ between groups. However, the intervention had a significant superior positive effect on the frequency of substance use (per substance using day) and on the readiness to change at 12 months (Barrowclough et al. 2010). These findings are in line with earlier mainly negative findings of another study comparing the efficacy of motivational interviewing/CBT ($N=65$) and treatment as usual ($N=65$) in psychotic patients with hazardous alcohol, cannabis and/or amphetamine abuse during the preceding month (Baker et al. 2006). A recently published single-blind randomized controlled trial again comparing motivational interviewing and cognitive behavioural therapy with standard clinical care in 110 recent-onset psychosis patients with comorbid cannabis use could yet not demonstrate a clinical benefit in terms of a reduction of the amount of cannabis use or the clinical outcome parameters (Barrowclough et al. 2014).

A recent Cochrane review included 32 randomized controlled trials comparing psychosocial

interventions for substance abuse with standard care in people with serious mental illness and could not reveal an overall superiority of the interventions (Hunt et al. 2013). However, a superiority could be observed in abstinence from alcohol (1 RCT), but not from other drugs. In summary, this Cochrane review questions the efficacy of specific intervention for this indication. Emerging problems in comparing trials (especially for preparing meta-analyses) are the heterogeneity of intervention, the relatively small sample sizes (not for the new trials), the different follow-up periods and the differences of the used drugs. It seems that earlier trials included more patients with alcohol abuse, whereas in new trials cannabis use is more frequent, and this could explain the shift in the reported superiority to more unspecific effects of specific interventions. Yet, in summary, there is only limited evidence that specific interventions have an effect on different outcome parameters in schizophrenia patients with comorbid substance abuse (*Category of Evidence C3, Level of Recommendation 4*). However, the results of single trials are encouraging and especially for comorbid alcohol abuse/dependency there is sufficient data to recommend specific interventions (*Category of Evidence B, Level of Recommendation 3*). For cannabis abuse/dependency there is no evidence for specific interventions. The APA guidelines (Lehman et al. 2004), the APA Watch Guidelines (Dixon et al. 2009) and the PORT guidelines (Kreyenbuhl et al. 2010) recommend special interventions with motivational and behavioural components for patients with schizophrenia and comorbid substance use disorder.

Pharmacological treatment

Recommendations for the pharmacological treatment of comorbid substance abuse in schizophrenia could be separated into recommendation for:

- (1) specific antipsychotic treatment in this population to improve psychopathology and
- (2) for specific treatment of comorbid substance abuse (e.g., alcohol, tobacco, illegal substances).

It should be considered that most antipsychotic treatment trials excluded patients with a comorbid drug abuse/dependency. In general, antipsychotics with extensive anticholinergic side-effects should be avoided since the anticholinergic effects of the abused substances could be consequently be potentiated (see the evaluation of clozapine below). Additional positive symptoms caused by substances usually remit with abstinence. Hence, schizophrenia patients with concomitant substance

use do not require higher doses of antipsychotics than those without comorbid substance abuse (Siris 1990; Wilkins 1997; Lehman et al. 2004; Falkai et al. 2005). Patients need to be informed that side-effects such as sedation and dizziness can be aggravated when antipsychotics are co-administered with all kinds of legal and illegal drugs (Lehman et al. 2004).

Antipsychotics

In general, the available studies regarding antipsychotic treatment in schizophrenia and comorbid substance abuse are of small sample size. In the last version of the WFSBP guidelines (Falkai et al. 2005), inconclusive data were provided from open-trials and case reports showing that treatment with flupentixol decanoate reduced alcohol consumption and craving together with a slight improvement in psychopathology in schizophrenia patients with dual diagnosis (Soyka et al. 1995; Soyka et al. 2003). However, one study with 281 patients suffering from severe alcohol dependency compared flupentixol decanoate with placebo and showed more relapses in the verum group (Wiesbeck et al. 2001). An improvement of both, psychopathology and substance intake (alcohol, cocaine, marijuana, benzodiazepines and amphetamines) has been shown in two further studies discussed in the previous version of these guidelines (Falkai et al. 2005).

For SGAs, we concluded in 2005 that clozapine has the largest body of evidence for the treatment of schizophrenia patients with comorbid substance abuse. In case records, case series, retrospective analysis of treatment-resistant patients and cross-sectional studies, in most studies clozapine resulted in reduced substance intake and concomitant improvement in schizophrenia symptoms. Furthermore, we provided limited evidence for the efficacy of risperidone, olanzapine and of tricyclic antidepressants in schizophrenia patients with comorbid substance abuse to reduce the frequency and amount of drug consumption (Falkai et al. 2005). Since 2005, three systematic reviews have been published which specifically investigated antipsychotic trials in schizophrenia patients with dual diagnosis (Wobrock et al. 2008; Zhornitsky et al. 2010; Kelly et al. 2012;). Zhornitsky and co-workers identified 43 studies, of which 23 included patients with concomitant psychosis (10 case-control and 13 randomized studies). When excluding studies with bipolar patients and trials focussing on tobacco dependency only five RCTs in schizophrenia patients with comorbid stimulants, cannabis and alcohol abuse could be identified in this review (Zhornitsky et al. 2010). The main findings of this review can be summarized as follows:

- the best evidence is available for clozapine in schizophrenia patients with comorbid alcohol use disorder for the reduction of alcohol use;
- the evidence for clozapine for reduced consumption rates in schizophrenia patients with cannabis use disorder is limited;
- other SGAs (quetiapine, olanzapine and risperidone) may lead to improvements in alcohol (and cannabis) abuse; and
- the efficacy of SGAs on stimulant dependency is not obvious from positive and negative studies.

The review of Kelly et al. (2012) adds to the former evidence one secondary analysis of an RCT in first-episode schizophrenia patients indicating no difference between olanzapine and risperidone on cravings or use of cannabis in patients with co-occurring lifetime diagnosis of cannabis use disorders (Sevy et al. 2011). In a more recent pilot RCT ($N = 30$) patients with schizophrenia and cannabis abuse/dependence were treated either with ziprasidone or with clozapine and followed-up for up to 12 months. In both groups cannabis use was reduced while clozapine treatment was associated with less positive symptoms, more side-effects and poorer compliance with treatment (Schnell et al. 2014). For second-generation long-acting injectables (LAI) there is one open label, rater-blinded, RCT available comparing risperidone microspheres 47.2 mg/2 weeks and zuclopenthixol decanoate 200 mg/3 weeks treatment for 6 months in a sample of schizophrenia patients ($N = 115$) with alcohol and/or drug abuse or dependence (Rubio et al. 2006). There was significantly less positive urine drug tests, longer time until relapse to illicit drug use, and a greater improvement of positive, negative, general and total symptom measures on the PANSS with risperidone microspheres while treatment with zuclopenthixol decanoate was associated with more motor side-effects (Rubio et al. 2006). A reanalysis of a more recent long-term randomized trial in schizophrenia patients could demonstrate that white patients benefited more from LAI (risperidone microspheres) than the other groups (oral antipsychotics to the psychiatrist's choice) on substance abuse outcomes (Leatherman et al. 2014) pointing towards a preferred use of LAI in this special population.

In addition, other studies indicate that both FGAs (haloperidol) and SGAs (olanzapine, risperidone, quetiapine) can have a beneficial effect on craving in schizophrenia patients with comorbid cocaine abuse (Smelson et al. 2002, 2006; Tsuang et al. 2002; Weisman 2003; Sayers et al. 2005).

Summary statements

- Clozapine seems to be effective for the reduction of craving and substance intake in patients with a dual diagnosis of schizophrenia and alcohol use disorder (*Category of Evidence B, Level of Recommendation 3*) and other substance use disorder (*Category of Evidence C3, Level of Recommendation 4*). It has to be considered that due to the high non-compliance in this patient group the long titration period when initiating treatment again may limit the use of clozapine. Special caution is required as patients with alcohol use disorders are at-risk to develop diseases of the blood-forming system (e.g., macrocytic anaemia, but also pancytopenia) or depression of bone marrow that may increase the risk for clozapine-induced agranulocytosis. Furthermore, comorbid alcohol use disorder may potentiate clozapine-induced cardiac toxicity.
- Some antipsychotics seem to be effective in patients with a dual diagnosis of schizophrenia and alcohol use disorder (*Category of Evidence C3, Level of Recommendation 4*) for the reduction of craving and substance intake.
- Other antipsychotics (FGA and SGA) show limited positive evidence in schizophrenia patients with cocaine use disorder (*Category of Evidence B, Level of Recommendation 3*) for the reduction of craving and substance intake as detailed above.
- An inconsistent superiority of SGAs compared to FGAs in the reduction of craving and the amount of the used substance can be assumed (*Category of Evidence C3, Level of Recommendation 4*).
- Due to the high non-compliance in dual diagnosis patients the preferred use of long-acting injectables is useful (*Category of evidence C3, Level of Recommendation 4*).

Anticraving agents

There is only very limited data regarding anticraving agents for the treatment of comorbid alcohol dependency in schizophrenia patients. One case report (74-year-old female schizophrenia patient) indicates a beneficial effect of acamprosate in patients with a dual-diagnosis of schizophrenia and alcohol dependency (Tek et al. 2008). ClinicalTrials.gov lists one 2-week, randomized, double blind, placebo trial (NCT00463346, planned sample size = 30) which investigates the efficacy of add-on acamprosate

treatment in schizophrenia patients with a comorbid alcohol dependency. For naltrexone, ClinicalTrials.gov lists two trials investigating the efficacy of naltrexone for this indication. Both trials (NCT00453609; NCT00145847) have been completed but the results have not been reported. In a pilot RCT ($N = 31$) add-on naltrexone treatment leads to significantly fewer drinking days, heavy drinking days (> 5 drinks) and less reported craving compared to placebo, while there was no difference in psychopathology between groups (Petrakis et al. 2004). However, there is only very limited evidence for the application of acamprosate or naltrexone for this indication and a general recommendation is not possible. One case report showed reduced craving for alcohol and a reduced substance intake after treatment with baclofen in a schizophrenia patient with a dual-diagnosis (Agabio et al. 2007).

Other agents

Some earlier studies indicate that the tricyclic antidepressant desipramine, administered adjunctive to antipsychotic therapy, can reduce craving (Ziedonis et al. 1992) and cocaine use (Wilkins 1997) in cocaine-dependent schizophrenia patients. The additional administration of imipramine in dysphoric schizophrenia patients with comorbid cocaine and cannabis abuse was associated with a reduced use of cocaine but not of cannabis, while depressive symptoms did not improve and psychotic symptoms worsened in one patient (Siris et al. 1993). A case series in which treatment-resistant schizophrenia patients with comorbid alcohol use disorder were treated with lamotrigine in combination with clozapine found a significant reduction of alcohol consumption and craving (Kalyoncu et al. 2005). However, because of their anticholinergic effects, treatment with tricyclic antidepressants should not be initiated until drug detoxification is completed. Other adverse effects of treatment with TCAs may be the precipitation of hypertensive crises during concomitant use of substances with adrenergic stimulation (Falkai et al. 2005). In summary, there is only very limited evidence based on earlier studies to recommend the application of TCAs for cocaine-dependent schizophrenia patients to reduce cocaine consumption, a general recommendation for TCAs in schizophrenia patients with comorbid substance abuse is not possible.

Tobacco dependency

Smoking rates of up to 90% have been reported in schizophrenia patients and a biological link between tobacco dependence and schizophrenia has been

related in many studies (Dome et al. 2010; D'Souza et al. 2012). As smoking contributes to metabolic syndrome, cardiovascular disorder and other somatic illness and hence schizophrenia has an increased risk for these somatic comorbidities (De Hert et al. 2011; Hasan et al. 2013), the pharmacological and psychosocial treatment of tobacco dependency receives more and more attention. At the same time, the APA stated that smoking cessation is a critical health challenge for individuals with schizophrenia (Dixon et al. 2009).

The 2009 published APA Guideline Watch: Practice guideline for the treatment of patients with schizophrenia (Dixon et al. 2009) recommends on the basis of several randomized, placebo-controlled trials the application of bupropion, bupropion plus nicotine replacement therapy and as well as bupropion plus CBT for smoking reduction in schizophrenia. However, the authors suggest a more extended pharmacological treatment in patients aiming to reduce smoking rates as the cited studies reported more relapse following study termination (Dixon et al. 2009). The PORT guidelines (Buchanan et al. 2010; Kreyenbuhl et al. 2010) also recommend the application of bupropion with or without nicotine replacement therapy accompanied by a psychosocial intervention in schizophrenia patients who want to reduce or quit smoking. The EPA Guidance on tobacco dependence and strategies for smoking cessation in people with mental illness (Rüther et al. 2014) recommends psychosocial intervention, nicotine replacement therapy, bupropion and varenicline for the treatment of tobacco dependency in schizophrenia. One recent Cochrane meta-analysis investigated different interventions for smoking cessation and reduction in individuals with schizophrenia. The authors included 34 trials of which seven trials compared bupropion with placebo and two trials compared varenicline with placebo (Tsoi et al. 2013). This Cochrane review showed that bupropion increases smoking abstinence rates in schizophrenia patients without worsening the psychopathology. Furthermore, varenicline also has a beneficial effect on smoking rates in schizophrenia patients, but the authors illustrate clearly that psychiatric adverse effects cannot be ruled out (Tsoi et al. 2013). An updated systematic review and meta-analysis included six trials with only schizophrenia and one trial with schizophrenia and bipolar disorder investigated the efficacy and safety of varenicline regarding the reduction of smoking rates in schizophrenia compared to placebo. Despite some positive source studies, this meta-analysis (seven studies, 352 schizophrenia patients in total) could not detect a superiority of varenicline adjuvant therapy compared to placebo for smoking cessation in schizophrenia (Kishi et al. 2014). Furthermore, the authors could

not find an increased risk for suicidal ideation and depression between varenicline and placebo which confirms the good tolerability of varenicline (Kishi et al. 2014). This consequently confirms the safety findings from one previous systematic review (Cerimele et al. 2012). Finally, one small double-blind randomized clinical trial compared the allosteric modulator of nicotine acetylcholine receptors galantamine ($N=18$) with placebo ($N=25$) and could not find an effect on smoking behaviour in schizophrenia patients (Kelly et al. 2008).

Summary statements for smoking cessation

- Smoking cessation should only be initiated in patients with stable schizophrenia and not in the acute phase of illness (*Good Clinical Practice*).
- Nicotine replacement therapy can be recommended with good evidence for this indication (*Category of Evidence B, Level of Recommendation 3*): it should be considered that the EPA guidelines (Rüther et al. 2014) recommend nicotine replacement therapy as first-line therapy for all smokers.
- The data regarding cognitive and other psychosocial interventions are inconclusive, nevertheless should these interventions be considered in all schizophrenia patients who want to reduce or quit smoking (*Category of Evidence C3, Level of Recommendation 4*).
- Bupropion should be offered to schizophrenia patients who want to reduce or quit smoking (*Category of Evidence B, Level of Recommendation 3*); the potential additive risk for lowering the epileptic threshold should be taken into account (EEG should be controlled, especially when combined with clozapine).
- The data regarding varenicline is inconclusive and due to the negative meta-analysis and the limited sample sizes of the source studies no recommendation is possible until large multi-centric trials become available (*Category of Evidence D, Level of Recommendation 5*).

Pregnancy and lactation

In contrast to other sections of these guidelines, the section pregnancy and lactation will only be based on other guidelines and systematic reviews of case series and reports since studies with a sufficient controlled design are obviously not available. The APA guidelines (Lehman et al. 2004) and the DGPPN guidelines

(DGPPN 2006) provide specific, but limited chapters regarding pregnancy and lactation in schizophrenia patients. One should bear in mind that women with schizophrenia have a higher rate of unwanted pregnancy and high rates of obstetric problems (Miller 1997; Bennedsen 1998). One sample of 2096 births by 1428 mothers with schizophrenia and 1,555,975 births in the general publications indicates an increased risk for stillbirth, infant death, preterm delivery, low birth weight, and small-for-gestational-age among the offspring of women with schizophrenia (Nilsson et al. 2002). However, after statistical control of the high smoking rates during pregnancy (two-fold higher than in the normal population) and for other maternal risk factors (single motherhood, maternal age, parity, maternal education, mothers' country of birth and pregnancy-induced hypertensive diseases), the risk estimates were reduced markedly (Nilsson et al. 2002). This confirms findings from earlier studies and reviews showing an increased risk of obstetric complications (Modrzewska 1980; Sacker et al. 1996) and it indicates that comorbidities and other risk factors significantly contribute to the obstetric complications in pregnant schizophrenia women (Bennedsen 1998). The increased risk of obstetric complications has been established by many case-control studies (e.g., Byrne et al. 2007). Furthermore, the risk of stillbirth and infant death among 2230 children of women with schizophrenia were compared with the risks among 123,544 children in the general population, and the risk of congenital malformations among 746 children of women with schizophrenia were compared with the risk among 56,106 children in the general population in one study (Bennedsen et al. 2001). The results of this study indicate an increase risk for sudden infant syndrome and for congenital malformations, but not for stillbirth or neonatal death. However, the authors limitate their findings as the relative risks have not been corrected for the aforementioned risk factors like smoking, other substance abuse or type of administered medication (Bennedsen et al. 2001). A recently published prospective cohort study compared 561 pregnant women using SGAs with 284 pregnant women using FGAs and 1122 pregnant women using drugs known not to be harmful to the fetus (Habermann et al. 2013). However, major malformation rates due to SGA exposure were superior to comparison cohort II (OR 2.17) (atrial and ventricular septal defects were the most frequently observed). Furthermore, the prenatal exposure to FGAs was associated with a higher rate of postnatal disorders (21.6%) compared to the SGA exposure (15.6%) and to the comparison cohort II (4.2%). Finally, preterm birth and low birth weight could be observed more commonly in infants exposed to FGAs (Habermann et al. 2013).

In summary, an overall teratogenic risk for SGAs was not found and the number of stillbirths and neonatal deaths were within the reference ranges. The SGA and FGA group had a higher cumulative incidence for elective pregnancy termination with no differences in spontaneous abortions across all three groups (Habermann et al. 2013). Another recent study specifically reported the after-birth conditions of 142 children who were exposed to antipsychotics and showed that 18% were born preterm, that 43% required special nursery or intensive care, that 37% had a respiratory distress syndrome and that 15% showed signs of a drug withdrawal (Kulkarni et al. 2014). One descriptive cohort study using a prospectively collected database investigated 133 women exposed to SGAs and other psychotropic drugs and 133 matched controls. A total of 137 mother-child pairs were exposed to SGAs in monotherapy and 96 received a treatment with more than one psychoactive drug. Polytherapy was associated with significantly higher pre-pregnancy weight, with more associated comorbidities and instrumental deliveries, and with more gestational age neonates (Sadowski et al. 2013). The neonates who were exposed to polypharmacy had more complications (premature born, higher need for intensive care unit, more neonatal adaptation signs and more congenital malformations) than those who were exposed to a monotherapy (Sadowski et al. 2013). These findings indicate that polypharmacy results in more complications during pregnancy for the mother and the unborn foetus compared to monotherapy. Every pharmacological treatment (and thus antipsychotic treatment) in pregnancy and lactation is associated with an elevated potential risk for obstetric, teratogenic, neurobehavioural and neonatal complications (McCauley-Elsom et al. 2007). On the other hand, an untreated psychosis of the mother is associated with an increased risk for pregnancy complications or difficulties in care after birth. Different systematic and literature reviews have analysed in detail the maternal and fetal effects of antipsychotic drugs in pregnancy (Einarson et al. 2009; Galbally et al. 2014). These reviews indicate an increased risk for prematurity, reduced or elevated birth weight, gestational diabetes or abnormal muscle movements, but illustrate that no definitive association could be made specifically with the antipsychotic treatment. According to the APA (Lehman et al. 2004) guidelines, the antipsychotic treatment of a pregnant or lactation patient with schizophrenia has to consider two issues:

- risks of various psychotropic medications (here antipsychotics) to the foetus, newborn, and breast-fed infant;
- adequacy of prenatal care.

The American Academy of Pediatrics in their guidance paper “Use of psychoactive medication during pregnancy and possible effects on the foetus and newborn” stated that pharmacological therapy is needed for the management of psychiatric disorders and that each decision requires psychiatric and obstetric advice (Pediatrics 2000).

In clinical practice, principally four different situations need to be considered with respect to antipsychotic treatment in pregnancy and lactation:

- Females with schizophrenia on stable antipsychotic medication who wish to have children.
- Females with schizophrenia on stable antipsychotic medication who become pregnant.
- Females who develop for the first time a psychosis during pregnancy or maternity.
- Females who develop a relapse of psychosis during pregnancy or maternity.

One systematic review has summarized four different potential risks for the mother-child pair associated with an exposure to antipsychotics during early or late pregnancy (Gentile 2010):

- Fetal major malformations (structural teratogenicity).
- Perinatal complications (neonatal toxicity).
- Postnatal behavioral sequelae (behavioral toxicity).
- Gestational complications.

Additionally, the possible behavioral consequences for child development should be kept in mind.

General aspects of treatment

The following section compiles and extends general recommendations from several empirical and systematic reviews and from different guidelines (Lehman et al. 2004; DGPPN 2006; McCauley-Elsom et al. 2007; Galbally et al. 2010, 2014; Gentile 2010; Seeman 2013). Thus, all recommendations are based on the opinion of experts in the field or on clinical experience (*Category of Evidence C3, Level of Recommendation 4*).

- The management of pregnancy and lactation in females with schizophrenia must be performed by a multi-professional team including psychiatrists, gynaecologists, paediatricians and midwives and must involve the family intimately. Specific support is recommended in cases where families are unable to cooperate or are in need of social support.
- Other factors potentially harmful for the foetus (e.g., concomitant substance abuse) need to be improved.

- Five mg folate per day should be prescribed 3 months before conception and throughout the whole pregnancy.
- It is necessary that all patients and their partners are informed about the risks and benefits of an antipsychotic treatment in pregnancy and lactation and a written informed consent should be obtained if possible. Furthermore, respective fears and reservations and restraints should be addressed to by a psychoeducational interview. Especially a relative risks for teratogenicity and malformations in pregnancy without any treatment should be well explained and set into correlation with the relative risks associated to an antipsychotic treatment.
- The complete course of pregnancy regarding maternal complications (e.g., gestational diabetes mellitus) or complications of the unborn foetus should be monitored and documented closely. This includes periodic health examinations, regular blood sampling, glucose tolerance testing (especially when certain SGAs with unfavorable metabolic profile are prescribed) and ultrasound assessments.
- If the mother refuses to accept a treatment and the psychotic symptoms are a danger for her or the foetus life, involuntary treatment needs to be considered respecting the local ethical and legal frameworks.
- The childbirth should take place in specialised centres with experience in the field and with the possibility of contacting psychiatrists and pediatricians at any time. These centres should have a neonatal intensive care unit as antipsychotic treatment before birth is associated with different postnatal complications (respiratory distress, withdrawal symptoms) and may require intensive care or special nursery.
- After birth, a good mother–child relationship should be fostered by offering psychosocial support if necessary.
- Despite the relatively low risk for early or late complications, a follow-up of children born by mothers who received antipsychotic treatments regarding the child development and possible complications (e.g., early complications like respiratory distress or late complications like early metabolic syndrome or developmental delays) should be carried out.
- Polypharmacy, especially with mood stabilizers or SSRIs, should be avoided.

Anitpsychotic treatment in pregnancy and lactation

Recommendation regarding antipsychotic treatment in pregnancy must follow a more prescriptive standard than in routine clinical care. As outlined above, controlled studies of any psychotropic drug risk during pregnancy are for ethical reasons not available (Lehman et al. 2004). As stated in a Cochrane collaboration systematic review, readers should be aware that “current guidelines and clinical practice for the use of antipsychotic drugs in women with non-affective disorders during pregnancy and postpartum are not based on evidence from randomized controlled trials” (Webb et al. 2004). One should bear in mind that mood stabilizers, certain antidepressants and benzodiazepines have a higher likelihood for fetal malformations and behavioral effects than antipsychotics (Lehman et al., 2004). Some general aspects for the antipsychotic treatment in pregnancy and lactation should be considered (Lehman et al. 2004; DGPPN 2006; Barnes et al. 2011) (*Category of Evidence C3, Level of Recommendation 4*):

- If no contraindications are available, antipsychotics that have been shown to allow a sufficient control of schizophrenia symptoms in a given patient should be used primarily.
- If possible and clinically tolerable, the introduction of an antipsychotic should be delayed to the second or third trimester as the highest risk for malformations lies in the first trimester. If clinically indicated, antipsychotics can be introduced in the first trimester but must follow a strict risk/benefit assessment.
- The minimal effective dose of the respective antipsychotic should be used and combination treatments should be avoided. Before initiation of an antipsychotic treatment, all psychosocial treatments should have been fully exploited.
- Therapeutic Drug Monitoring should be performed to take into account changes in the metabolism of the mother during pregnancy and lactation.
- After a clear benefit/risk assessment, it is not recommended to stop antipsychotic medication abruptly, as this increases the risk for relapse and hence the risk for obstetric complication or harm for the foetus.
- The use of oral medication to allow a flexible dosing scheme is recommended – women who are stable on a depot medication should not be switched to an oral medication if not necessary.

Recommendations (see Table V) for specific antipsychotic drugs cannot reach an evidence level higher than C3 (Category of Evidence C3, Level of Recommendation 4; expert opinion/clinical experience). The FDA introduced in 1979 the pregnancy category (or pregnancy risk category) for the assessments of the fetal risks during a pharmacological exposure during the mothers pregnancy. More information regarding specific antipsychotics can be found in the “List of Pregnancy Exposure Registries” on the www.fda.gov website. The information regarding safety and applicability of the specific antipsychotics described in the following sections has been extracted from systematic reviews (McCauley-Elsom et al. 2007; Gentile 2010) and from national guidelines (Lehman et al. 2004; DGPPN 2006; Barnes et al. 2011).

FGAs in pregnancy

Haloperidol is one of the best approved FGAs in schizophrenia treatment which has also been used in clinical practice for the treatment of psychosis during pregnancy – in this specific condition the most experience seems to be available for this agent. The lowest necessary dosage of haloperidol can be considered for the application during pregnancy (low dose regimen). Despite the great clinical experience with other FGAs, no other drug from this group should be used for the initiation of treatment during pregnancy and lactation.

Table V. Recommendations for the use of antipsychotics in pregnancy and lactation.

| Antipsychotic | Category of evidence ^a | Recommendation ^b |
|---|-----------------------------------|-----------------------------|
| <i>Pregnancy</i> | | |
| Haloperidol | C3 | 4 |
| Risperidone | C3 | 4 |
| Olanzapine | C3 | 4 |
| Quetiapine | C3 | 4 |
| Clozapine | Not recommended | 5 |
| Other SGAs | F | – |
| <i>Breastfeeding</i> | | |
| If possible, avoid breastfeeding during antipsychotic treatment | C3 | 4 |
| Olanzapine | C3 | 4 |
| Chlorpromazine | C3 | 4 |
| Clozapine | Not recommended | 5 |
| Zuclopenthixol | Not recommended | 5 |

^aCategory of evidence: Category of evidence where A = full evidence from controlled studies (see Table I).

^bSafety rating = recommendation grade derived from categories of evidence and additional aspects of safety, tolerability, and interaction potential. GCP, Good Clinical Practice. Please see main text for more details.

SGAs in pregnancy

Among the SGAs the most experience is available for olanzapine and it can be considered as a treatment possibility in pregnancy. However the increased risk for gestational diabetes and the associated secondary diseases needs to be taken into account. Some cases of neural tube defects have been reported with olanzapine (Gentile 2010). There is less experience regarding the use of risperidone in pregnancy. However, it can be considered as a treatment possibility for pregnancy but especially potential motor side-effects of the newborn must be monitored. Quetiapine seems to be related to olanzapine, but the clinical experience is not as good. However, quetiapine can also be considered as a treatment option for pregnancy. Due to its specific side-effect profile (especially agranulocytosis, seizure induction, metabolic effects) and a high proportion of perinatal complications (e.g., floppy infant syndrome, neonatal hypoxic encephalopathy), clozapine should not be used in pregnancy. Other SGAs should not be introduced in cases of schizophrenia associated pregnancy as the clinical experience is low. There is not enough sufficient data to give recommendations for other SGAs.

Every switch in antipsychotic treatment is associated with an increased risk for relapse (Hasan et al. 2012). And as pregnant women with schizophrenia already have a high risk to discontinue medication with a consecutive relapse (Spielvogel et al. 2010), an ongoing antipsychotic medication with any SGA should not be stopped without any clear safety reasons.

Breastfeeding

A number of guidelines do not recommend breastfeeding during an antipsychotic treatment (Lehman et al. 2004; DGPPN 2006). This statement has amongst other been based on the limited safety evidence (DGPPN 2006). However, literature reviews do not principally rule out the possibility of breastfeeding during antipsychotic intake (Usher et al. 2005; Seeman 2013). One systematic review which included studies from 1950 to 2008 was not able to draw conclusions regarding the risk/benefit of breastfeeding during antipsychotic treatment, but nevertheless stated explicitly that clozapine and olanzapine should not be used during breastfeeding (Gentile 2008). One recently published meta-analytic review included four prospective studies, 12 case series, 28 case reports and one pharmaceutical registry in order to investigate the impact of antipsychotic exposure during breastfeeding on the newborn child. The authors classified quetiapine and olanzapine as acceptable for breastfeeding. Chlorpromazine, haloperidol, risperidone and zuclopenthixol were only classified as possible if medical supervision was

confirmed. For all other antipsychotics, breastfeeding was not recommended (Klinger et al. 2013).

One systematic review on the basis of a extensive bibliographic search in Medline (1967–2008), Embase (1975–July) and PsycINFO (1967–2008) showed that antipsychotics represent just the class of psychoactive drugs with the smallest number of studies regarding the application during breastfeeding (Fortinguerra et al. 2009). The authors of this review recommend chlorpromazine and olanzapine as the first-choice drugs for psychosis in breastfeeding mothers since these antipsychotics have the lowest degree of excretion into breast milk (Fortinguerra et al. 2009). Due to their high relative infant dosage clozapine and sulpiride have been rated to be contraindicated during breastfeeding (Fortinguerra et al. 2009). In this context it seems necessary to mention that all psychotropic drugs are extracted into breast milk, but that the degree of extraction is dependent on the maternal dosage, the application frequency, the maternal absorption rate, the diffusion from maternal circulation into breast milk, the rate of the maternal drug metabolism and the absorption rates of the infant (Fortinguerra et al. 2009).

In general, the benefits of the mother–child interaction following breast-feeding need to be weighted against the potential harm of the newborn's antipsychotic exposure during breastfeeding. Another factor that needs to be considered is the risk of untreated psychosis in mothers who would actually like to breast feed. Due to the limited safety data, we do not recommend antipsychotic treatment during breastfeeding in general. However, in individual cases, the psychological risk of not breastfeeding for the woman must be weighed against the risk for the newborn's exposition to antipsychotics. If the risk/benefit ratio is favourable breast-feeding can be performed under continuous paediatric examinations of the child.

Conclusions

This update of the WFSBP guidelines for the biological treatment of schizophrenia summarizes the available evidence in the field regarding the following clinically relevant treatment circumstances: depression, suicidality, substance use disorders and pregnancy/lactation. Despite the great impact of depressive symptoms, suicidality and substance use disorder on the outcome and course of schizophrenia there is surprisingly few data for clear evidence-based recommendations based on randomized controlled trials. However, despite the lack of well-conducted multicentric clinical trials there is sufficient evidence from reviews, small studies and other sources for clinically applicable recommendations. Psychiatrists

should be aware that comorbid depression, suicidal-ity and substance use disorder further increases the already high mortality of schizophrenia. Therefore, these conditions need to be diagnosed correctly, treated quickly and with utmost care.

Pregnancy and lactation in women with schizophrenia represents a specific challenge for different medical fields with a need for intensive cooperation to provide the best care for these patients. Thus, interdisciplinarity and an optimal flow of information are the main keys for a successful treatment of schizophrenia during pregnancy and lactation. Obviously, no controlled studies are available for the use of antipsychotics in pregnancy and lactation. However, the data for antipsychotic treatment in pregnancy is sufficient to give clinically applicable recommendations. Apart from general considerations, certain FGAs and SGAs should be favoured compared to others. For breastfeeding there is far too little data available, so that all recommendations must be considered as limited.

In summary, the recommendations of this guideline expose a clear gap in evidence regarding specific, but nevertheless clinically relevant treatment situations in schizophrenia. To improve the long-term care of patients with schizophrenia, more research is needed in the here discussed scope. Since it cannot be expected that the pharmaceutical industry is likely to make great research efforts in these areas it is the challenge of clinicians and national and international academic institutions to perform the necessary studies and adequate acquire funding. Without these researches there will be no step forward in the care of schizophrenia.

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Statement of Interest

Alkomiet Hasan has been invited to scientific meetings by Lundbeck, Janssen-Cilag, and Pfizer, and he received paid speakership by Desitin, Otsuka and the Federal Union of German Associations of Pharmacists. He was member of the Roche Advisory Board.

Peter Falkai was the honorary speaker for Janssen-Cilag, AstraZeneca, Eli Lilly, Bristol-Myers-Squibb, Lundbeck, Pfizer, Bayer Vital, SmithKline Beecham, Wyeth, and Essex. During the last 5 years, but not presently, he was a member of the advisory boards of Janssen-Cilag, AstraZeneca, Eli Lilly, and Lundbeck. Thomas Wobrock was the honorary speaker for Alpine Biomed, AstraZeneca, Cerebromed, Bristol-Myers-Squibb, Eli Lilly, I3G, Janssen-Cilag, Novartis, Lundbeck, Sanofi-Aventis, Otsuka, and Pfizer, and has accepted travel or hospitality not related to a speaking engagement from AstraZeneca, Bristol-Myers-Squibb, Eli Lilly, Janssen-Cilag, and Sanofi-Synthelabo; he is a member of the advisory board of Janssen-Cilag and has received a research grant from AstraZeneca, I3G, and AOK (health insurance company). Jeffrey Liebermann was/is a member of the advisory boards of Bioline, Intracellular Therapies, Alkermes, Lilly and Pierre Fabre. He received research support/grants by Allon, Glaxo-SmithKline, Lilly, Merck, Novartis, Pfizer, Psychogenics, LTD, Sepracor and Targacept. He holds a patent by Repligen. Birte Glenthøj is leader of a Lundbeck Foundation Center of Excellence for Clinical Intervention and Neuropsychiatric Schizophrenia Research (CINS) which is partially financed by an independent grant from the Lundbeck Foundation based on international review and partially financed by the Mental Health Services in the Capital Region of Denmark, the University of Copenhagen, and other foundations. She has nothing else to declare. Wagner F. Gattaz reports no conflict of interest. Florence Thibaut is a member of the Sertindol Study International Safety Committee. Hans-Jürgen Möller received honoraria for lectures or for advisory activities or received grants by the following pharmaceutical companies: Astra-Zeneca, Eli Lilly, Janssen, Lundbeck, Pfizer, Schwabe, Servier, Otsuka and Takeda. He was president or in the Executive Board of the following organisations: CINP, ECNP, WFSBP, EPA and chairman of the WPA-section on Pharmacopsychiatry.

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