ACUTE TREATMENT OF SCHIZOPHRENIA: INTRODUCTION TO THE WORD FEDERATION OF SOCIETIES OF BIOLOGICAL PSYCHIATRY GUIDELINES

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SUMMARY

    The goals and strategies of treatment in schizophrenia may vary according to the phase and severity of the illness. Antipsychotics remain the cornerstone in the acute phase treatment, in the long-term maintenance therapy and in the prevention of relapse of schizophrenia.

    This paper is intended to review the current practice in the management of the acute treatment of schizophrenia based on the recently published guidelines from the World Federation of Societies of Biological Psychiatry (WFSBP).

    Both first generation antipsychotics (FGAs) and second generation antipsychotics (SGAs) are effective in the acute treatment of schizophrenia and in relapse prevention. Clinicians must keep in mind that most patients are likely to require long-term, if not life-long, treatment which determines treatment strategy with an optimal balance between efficacy, side effects and compliance. In this regards, SGAs do have some advantages, but the risk of metabolic syndrome must be taken into account and carefully checked at regular intervals during the follow-up.

Key words: *neuroleptics – antipsychotics – schizophrenia - acute treatment - treatment resistance – FGAs - SGAs*

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INTRODUCTION

Schizophrenia is a chronic, severe, and disabling brain disorder. For a given patient, the first step is to make an accurate diagnosis. Once the diagnosis is established, it is critical to identify the targets of treatment, to have outcome measures that evaluate the effect of treatment and to have realistic expectations about the level of improvement that constitute successful treatment (APA 1997, 2004a). Treatment is aimed to alleviate or even eradicate symptoms, to optimize quality of life and social functioning and to promote and maintain recovery. Targets of treatment may include positive and negative symptoms, depression, substance use, social behavior, level of autonomy etc. Medical comorbid conditions may also be identified and treated. For each patient, a treatment plan must be formulated and implemented (type, modalities, setting), taking into account history of past and current treatments and response to them. Periodic reevaluation of the diagnosis and the treatment plan is necessary. Many patients will need a variety of types of treatments involving different clinicians who need to coordinate. A supportive therapeutic alliance allows the psychiatrist to get essential information about the patient and allows the patient to develop trust in the psychiatrist and the treatment. Identifying the patient's goals and relating them to treatment outcomes increases treatment adherence. The clinician may also identify practical barriers to the patient's ability to participate in treatment, such as cognitive impairments and inadequate social resources. Engagement of the family and other significant support persons, with the patient's permission, is recommended to further strengthen the therapeutic alliance (APA 2004a).

The goals and strategies of treatment may vary according to the phase and severity of illness. Antipsychotics remain the cornerstone in the acute phase treatment, in long-term maintenance therapy and in the prevention of relapse of schizophrenia.

This paper is intended to review the current practice in the management of the acute treatment of schizophrenia based on the recently published guidelines from the World Federation of Societies of Biological Psychiatry (WFSBP). These guidelines were prepared by the WFSBP Schizophrenia Task Force and reviewed by all Presidents of National Societies of Biological Psychiatry who are members of the WFSBP. They were published in the official journal of the WFSBP: The World Journal of Biological Psychiatry in 2012 (Hasan et al. 2012). The methods of literature research and data extraction used in the WFSBP schizophrenia guidelines were detailed in Hasan et al. (2012) and in Appendix 1 as regard to the definitions of the categories of evidence and the levels of recommendation.

In general, first generation antipsychotics (FGAs) are effective in the treatment of schizophrenia. Low-potency FGAs are inferior to high-potency FGAs such as haloperidol for the treatment of acute schizophrenia. Following the introduction of second generation anti-

psychotics (SGAs), patients and psychiatrists had hope of a new treatment period for schizophrenia. However, the postulated advantages (better efficacy for positive and negative symptoms, better quality of life and side effect profile) in comparison to FGAs, are discussed controversially. The different side effects of each drug and the personal vulnerability of a given patient have to be taken into account before choosing a certain antipsychotic. In the early stages of treatment, acute neurological side effects should be avoided. When long-term treatment is considered, neurological side effects need to be balanced against metabolic and other side effects. However, it is important to note that SGAs do not represent a homogenous class of drugs (Leucht et al. 2009) and that certain side effects cannot be considered as typical for the whole group of SGAs. Differences in the risk of specific side effects of antipsychotics are often predictable from the receptor binding profiles of the various agents. Some side effects result from receptor-mediated effects within the central nervous system (e.g., extrapyramidal side effects, hyperprolactinemia, sedation) or outside the central nervous system (e.g., constipation, hypotension), whereas other side effects are of unclear pathophysiology (e.g., weight gain, hyperglycemia) (DGPPN 2006). It is somehow important to note that both FGAs and SGAs, depending on their individual receptor binding profiles share neurological side effects (acute and long-term extrapyramidal symptoms, neuroleptic malignant symptoms), sedation, cardiovascular effects, weight gain, metabolic effects, anticholinergic, antiadrenergic and antihistaminergic effects, hyperprolactinemia and sexual dysfunctions.

ACUTE PHASE OF TREATMENT

In the acute phase of treatment (lasting weeks to months), which is defined by an acute psychotic episode, major goals are to develop an alliance with the patient and family, to prevent harm, control disturbed behavior, reduce the severity of psychosis and associated symptoms (e.g., agitation, aggressiveness, negative symptoms, affective symptoms), determine and address the factors that led to the occurrence of the acute episode and to obtain a rapid return to the best level of functioning.

The psychiatrist must consider that the degree of acceptance of medication and information about it varies according to the patient's cognitive capacity, the degree of the patient's denial of the illness, and efforts made by the psychiatrist to engage the patient and family in a collaborative treatment relationship (Lehman et al. 2004).

It is recommended by all guidelines that every patient have an initial evaluation as his (or her) clinical status allows, including complete psychiatric and general medical histories and physical and mental status examinations. Interviews of family members may be useful, unless the patient refuses. The most common

contributors to symptom relapse are antipsychotic medication nonadherence, substance use, and stressful life events, although relapses are not uncommon as a result of the natural course of the illness despite continuing treatment. Medical conditions that could contribute to symptom exacerbation can be evaluated by medical history, physical and neurological examination, and appropriate laboratory, electrophysiological, and radiological assessments. Measurement of body weight and vital signs (heart rate, blood pressure, temperature) is also recommended (APA 2004b). Other laboratory tests to evaluate health status include measurements of blood count, blood electrolytes, glucose, cholesterol, and triglycerides; tests of liver, renal, and thyroid function; and when indicated and permissible, determination of human immunodeficiency virus (HIV) status and a test for hepatitis C. Routine evaluation of substance use is also recommended as part of the medical evaluation. A pregnancy test should be considered for women with childbearing potential. In patients for whom the clinical picture is atypical or where there are abnormal findings from a routine examination, electroencephalogram, magnetic resonance imaging scan, or computed tomography scan may be indicated. The likelihood of dangerous and aggressive behavior or of suicidal behavior must also be evaluated.

Then it is recommended that pharmacological treatment be initiated promptly because acute psychotic exacerbations are associated with emotional distress, disruption to the patient's life, and a substantial risk of dangerous behaviors. Whenever it is possible, the physician should discuss the potential risks and benefits of the medication with the patient.

The most important question concerning the pharmacological treatment of schizophrenia is whether to treat initially and predominantly with SGAs (as recommended in nearly all guidelines published between 2004 and 2009) or to treat with FGAs. In the first version of the World Federation of Societies of Biological Psychiatry guidelines it was determined that SGAs generally seemed to be preferable, although all antipsychotics have their place in the treatment of acute schizophrenia. Today, there is some evidence that FGAs and SGAs are comparable with regard to efficacy and effectiveness (especially reduction of PANSS scores). However, certain SGAs have some advantages with regard to motor side effects in the acute phase of treatment (*Category of evidence A*).

We will make a distinction concerning the treatment of acute schizophrenia between first-episode patients and multi-episodes patients (relapse).

First-episode schizophrenia

Since the introduction of risperidone and olanzapine, followed by other SGAs, most guidelines have recommended the first-line use of SGAs for individuals with a newly diagnosed schizophrenia (DGPPN 2006, Lehman et al. 2004, NICE 2002, RANZCP 2005). This

recommendation was based on the drug's superior tolerability and the reduced risk of extrapyramidal symptoms, especially tardive dyskinesia. However, the outcomes of several new clinical trials, metaanalyses and clinical experience question the first line use of SGAs.

Concerning efficacy and effectiveness of the treatment of positive and negative symptoms in schizophrenia, it is difficult to show a difference between FGAs and SGAs. Nevertheless, all authors agree on the fact that a shorter duration of untreated psychosis was associated with better response to antipsychotic treatment (Perkins et al. 2005). In general, patients with first-episode schizophrenia seem to be more treatment responsive but also more sensitive to antipsychotic side effects than chronically ill patients. The choice of antipsychotic drug should be based on the drug's profile in terms of adverse effects and on each patient's individual risk of developing particular associated side effects. Therefore, antipsychotic treatment should be specifically tailored to each patient suffering from schizophrenia. FGAs have a higher risk of inducing EPS compared to SGAs, whereas metabolic and cardiovascular side effects seem to be more prominent using SGAs. First-episode schizophrenia patients carry an increased risk for developing neurological side effects which needs to be taken into consideration before starting treatment with FGAs.

Both FGAs and SGAs are recommended for the treatment of positive symptoms in first-episode schizophrenia patients (*Category of Evidence A, Recommendation grade 1/2,* see table 1). There are still few RCTs available comparing the efficacy or effectiveness of FGAs and SGAs in first-episode patients. The EUFEST-trial did not find a significant difference in symptomatic improvement when comparing SGAs with haloperidol. However, treatment discontinuations over 12 months were more frequent and motor side effects were more severe in the haloperidol group (Kahn et al. 2008). The Cochrane schizophrenia group consistently found no superior efficacy of SGAs versus FGAs in first-episode schizophrenia. Nevertheless lower extrapyramidal symptoms rates (reduced use of anticholinergics) were observed in patients treated with risperidone or olanzapine compared to haloperidol, and olanzapine revealed superior improvement in global psychopathology (Rummel et al. 2003). Therefore, in first-episode schizophrenia, SGAs might be favoured with regard to the reduced rate of neurological side effects and the finding of a reduced treatment discontinuation rate (*Category of evidence B/C, Recommendation grade 3/4*).

Concerning the use of FGAs, a treatment recommendation can only be confirmed for haloperidol (*Category of Evidence A, Recommendation grade 2*) since other FGAs display only limited evidence but the risk for motor side effects should be considered (*Category of Evidence C/D, Recommendation grades 4/5*).

Among the SGAs, risperidone, olanzapine and quetiapine (*Category of Evidence A, Recommendation grade 1*) could be recommended, where as other drugs have not been tested extensively (see table 1). Amisulpride and ziprasidone could be recommended (*Category of Evidence B, Recommendation grade 3*), but the psychiatrist prescribing these two drugs should be aware that this recommendation was based on the results of one study (EUFEST).

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

Table 1. Recommendations for the antipsychotic treatment in first-episode schizophrenia patients (Hasan et al. 2012)

Antipsychotic agent	Category of evidence	Recommendation
Olanzapine	A	1
Quetiapine	A	1
Risperidone	A	1
Clozapine	A	2
Haloperidol	A	2
Amisulpride	B	2
Aripiprazole	B	2
Ziprasidone	B	2
Asenapine*	F	–
Iloperidone*	F	–
Paliperidone*	F	–
Lurasidone*	F	–
Sertindole*	F	–
Zotepine*	F	–

Category of evidence: Category of evidence where A means full evidence from controlled studies (see Appendix 1).

Safety rating: recommendation grade derived from categories of evidence and additional aspects of safety, tolerability, and interaction potential (see Appendix 1).

Clozapine is highly effective in the treatment of first-episode patients, but because of its side effect profile it should be considered as recommendation grade 2.

* It can be assumed that these antipsychotics are effective in the treatment of first-episode schizophrenia, but the WFSBP could not identify any study to give an evidence-based recommendation.

The presence of comorbid medical conditions and potential interactions with other prescribed medications may also guide the choice of the medication.

Inpatient care is required if there is a significant risk of self-harm or aggression, if the level of support in the community or in the family is insufficient. In general, the treatment setting should be based on the least

restrictive environment (RANZCP 2005), but it should be adapted according to the individual patient's disease severity and level of aggressiveness.

As first-episode schizophrenia patients display a higher risk of developing side effects (Buchanan et al. 2010), they should be treated with lower antipsychotic dosages than chronically ill patients (*Category of Evidence A, Recommendation grade 1*). Based on the literature, the recommendation of a treatment at the lower end of the standard dose range is mostly confirmed for haloperidol (5 mg/day), risperidone (4 mg/day) and olanzapine (10 mg/day) (*Category of Evidence B, Recommendation grade 3*). For other antipsychotics, there is only sparse evidence for this treatment recommendation (*Category of Evidence C/D, Recommendation grades 4/5*). The best recommended dose is that which is both effective and not likely to cause side effects that are unpleasant and may affect long-term compliance. The dose may be titrated as quickly as tolerated to the target therapeutic dose unless there is evidence that the patient is having uncomfortable side effects. Monitoring the patient's clinical status for 2–4 weeks is necessary to evaluate the patient's response and tolerance to the treatment. During these weeks it is important to avoid premature dose increase for patients who are responding slowly. If the patient is not improving, it may be helpful to establish whether the lack of response can be explained by medication nonadherence, rapid medication metabolism, or poor absorption (APA 2004a).

Adjunctive medications are also frequently used to treat comorbid conditions in the acute phase. Benzodiazepines may be used to manage catatonic symptoms or anxiety and agitation until the antipsychotic has reached efficacy. Careful attention must be paid to potential drug-drug interactions, especially those related to metabolism by cytochrome P450 enzymes.

Psychosocial interventions in the acute phase are aimed at reducing stressful relationships or environment through clear, simple and coherent communications and expectations, a structured and predictable environment, low performance requirements and tolerant, nondemanding, supportive relationships with the psychiatrist and other members of the treatment team (APA 2004a). Providing information to the patient and the family on the nature and management of the illness which is appropriate to the patient's capacity to assimilate information is recommended. Patients can be encouraged to collaborate with the psychiatrist in selecting and adjusting the medication and other treatments provided. The acute phase is also the best time for the psychiatrist to initiate a relationship with family members, who are usually particularly concerned about the patient's disorder, disability, and prognosis during the acute phase and during hospitalization. Family members may be under considerable stress, particularly if the patient has been exhibiting dangerous behavior.

Acute exacerbation (relapse), multi-episode patients

In case of relapse, the selection of an antipsychotic medication is frequently guided by the patient's previous experience with antipsychotics, including symptom response, previous experience of side effects, and preferred route of medication administration.

It has been demonstrated that all FGAs (with the exception of mepazine and promazine) are superior to placebo in the treatment of an acute exacerbation of schizophrenia (Davis et al. 1989, Dixon et al. 1995, Kane & Marder 1993). Haloperidol is the most investigated FGA and its efficacy for the treatment of acute schizophrenia is evident (Irving et al. 2006) (*Category of Evidence A, Recommendation grade 2*). One Cochrane review displayed that low doses of haloperidol (3–7.5 mg/day) were not inferior to higher doses of haloperidol (7.5–15 mg/day), but caused fewer motor symptoms (Donnelly et al. 2010).

The efficacy of SGAs in the treatment of acute exacerbations of multi-episode schizophrenia patients has been shown in many trials and large RTCs (see table 2).

Table 2. Recommendations for the antipsychotic treatment of multi-episode patients (acute relapse) (Hasan et al. 2012)

Antipsychotic agent	Category of evidence	Recommendation
Amisulpride	A	1
Asenapine*	A	1/2
Aripiprazole	A	1
Clozapine	A	1/2
Haloperidol	A	2
Iloperidone*	A	1/2
Olanzapine	A	1
Paliperidone*	A	1/2
Quetiapine	A	1
Risperidone	A	1
Sertindole*	A	1/2
Ziprasidone	A	1
Lurasidone	B	3
Zotepine	B	3

Category of evidence: Category of evidence where A means full evidence from controlled studies (see Appendix 1).

Safety rating: recommendation grade derived from categories of evidence and additional aspects of safety, tolerability, and interaction potential (see Appendix 1).

*These drugs are not approved for the treatment of schizophrenia in all countries and therefore it should be generally considered as recommendation grade 2 in these countries.

Clozapine is highly effective in the treatment of multi-episode patients, but it is only recommended as a second line treatment due to its special side-effect profile.

Sertindole has a safety rating of 1, but due to its cardiovascular side effect profile the use is restricted in some countries. In these countries, it should be considered as recommendation grade 2 for legal reasons.

Table 3. Monitoring for patients on second-generation antipsychotics

	Baseline	4 Weeks	8 Weeks	12 Weeks	Annually
Personal/Family History	x				x
Weight (BMI)	x	x	x	x	x
Waist circumference	x				x
Blood pressure	x	x		x	x
Fasting plasma glucose	x			x	x
Fasting lipid profile	x			x	x
Blood cell count	x	x		x	x
ECG	x				x
EEG	x				x
Pregnancy test	x				

BMI: Body mass index; ECG: electrocardiogram; EEG: electroencephalogram (Hasan et al. 2012, modified according to APA 2004b)

Antipsychotic monotherapy is recommended across all guidelines in the initial treatment of acute schizophrenic episodes (APA 2004a, Buchanan et al. 2010, DGPPN 2006, NICE 2010, RANZCP 2005) (*Category of Evidence C, Recommendation grade 4*).

Antipsychotic medication choice should be guided by the side effect profile of the drug, the patient's experience with certain side effects, the patient's previous response experience with certain anti-psychotics, and potential interactions with other prescribed medications (Buchanan et al. 2010, NICE 2010, RANZCP 2005). For FGAs and SGAs, the dose may be titrated as quickly as tolerated but as slowly as possible as regard to potential uncomfortable or dangerous side effects. The lowest effective dose should be used (*Category of Evidence C, Recommendation grade 4*).Clinicians must keep in mind that most patients may need lifelong treatment and so require treatment strategies with the optimal balance between efficacy and tolerability.

All SGAs and the established FGAs can be considered as treatment options for individuals experiencing an acute schizophrenic episode (*Category of Evidence A, Recommendation grade 1; for zotepine Category of Evidence B, Recommendation grade 3*).

Clozapine should be used in cases of treatment-resistant schizophrenia.

SGAs carry less risk of neurological side effects, especially tardive dyskinesia. Tardive dyskinesia is a severe side effect and the reduced risk for tardive dyskinesia favours the use of SGAs over FGAs (*Category of evidence C, Recommendation grade 4*). Furthermore, there might be some advantages of SGAs regarding treatment continuation, compliance and in other treatment domains (*Category of evidence C, Recommendation grade 4*). However, the increased risk of metabolic side effects following a treatment with certain SGAs (especially in the long-term treatment) as well as cardiovascular side effects need to be monitored and considered as part of any treatment decision (*Category of Evidence C, Recommendation grade 4,* see table 3). In long-term treatment (especially relapse prevention), there seems to be some superiority of certain SGAs and, therefore, initial treatment with an SGA in schizophrenia patients experiencing a relapse, could be favoured (*Category of evidence C, Recommendation grade 4*). Somehow, in routine clinical practice, if patients are currently achieving good control of their condition without unacceptable side effects with FGAs, changing from an FGA to an oral SGA is not recommended (Buchanan et al. 2010) (*Category of Evidence C, Recommendation grade 4*).

Before switching to another antipsychotic drug, a treatment trial with the optimal dose for each patient should last for at least 2 weeks, but not longer than 8 weeks, unless there is unacceptable tolerance or contraindication for the continuation of the present drug (*Category of Evidence C, Recommendation grade 4*) (Buchanan et al. 2010, Lehman et al. 2004, NICE 2002, 2010).

Frequent evaluations are necessary based on clinical status, especially during long-term treatment. The following monitoring intervals are suggested and need to be modified with regard to the administered antipsychotic and the national guidelines (see table 3). Patients treated with clozapine need a special monitoring including blood count and ECG.

The recommendation of daily dosages between 300 and 1000 mg CPZ equivalents for FGAs in the treatment of acute schizophrenia remains stable across the guidelines and across time (APA 1997, Buchanan et al. 2010, DGPPN 2006, Lehman et al. 2004, NICE 2010) (*Category of Evidence A, Recommendation grade 1*).

The following dosage ranges can be recommended for SGAs (Buchanan et al. 2010, NICE 2010, Schwartz & Stahl 2011):
- Amisulpride 200–800 mg/day;
- Aripiprazole 10–30 mg/day;
- Asenapine 5–20 mg/day;
- Clozapine 100–900 mg/day;
- Iloperidone 6–12 mg/day;
- Lurasidone 40–80 mg/day (as provided by the manufacturer);
- Olanzapine 10–20 mg/day;
- Paliperidone 6–12 mg/day;
- Quetiapine 300–800 mg/day;

- Risperidone 2–8 mg/day;
- Sertindole 12–24 mg/day;
- Ziprasidone 80–160 (180) mg/day;
- Zotepine 75–450 mg/day
(as provided by the manufacturer).

Specific situations

Treatment of primary and secondary negative symptoms

The differentiation of primary and secondary negative symptoms is of particular importance for the treatment of schizophrenia. Primary negative symptoms are considered a core symptom of schizophrenia, where as secondary negative symptoms are a consequence of positive symptoms (e.g., social withdrawal), neurological side effects (extrapyramidal side effects, acute dystonia, antipsychotic-induced parkinsonism and tardive dyskinesia), depressive symptoms (e.g., post-psychotic and antipsychotic-induced depression) or environmental factors (e.g., social understimulation due to hospitalization) (Carpenter et al. 1985). There are only few studies investigating the efficacy of antipsychotics in the treatment of primary negative symptoms. Most studies have investigated schizophrenia patients suffering from predominantly positive symptoms, with additional secondary negative symptoms. Until today, amisulpride is, apart from olanzapine, the only SGA that has been studied extensively in patients with primary/predominantly negative symptoms (*Category of Evidence A, Recommendation grade 1*). A general superiority of SGAs compared to FGAs for negative symptoms cannot be concluded, but SGAs are superior in the treatment of secondary negative symptoms (*Category of Evidence A, Recommendation grade 1*) and may be superior in the treatment of primary negative symptoms (*Category of Evidence B, Recommendation grade 3*).

The combination of antipsychotics administered with antidepressants might be promising (*Category of Evidence D, Recommendation grade 5*) and mirtazapine should be favoured (*Category of Evidence B, Recommendation grade 3*).

Treatment of cognitive symptoms

Cognitive functioning is a correlate of global and specific functional outcome in schizophrenia and cognitive impairments account for significant variance in measures of functional status (Green 1996).

A small and modest beneficial effect of antipsychotic medication in the treatment of neurocognitive disturbances can be assumed (*Category of Evidence B, Recommendation grade 3*). The comparison of FGAs and SGAs reveals inconclusive results with some studies favouring SGAs and some studies showing no difference between FGAs and SGAs. However, no study favours FGAs and therefore, a predominant use of SGAs can be recommended with limited evidence (*Category of Evidence C, Recommendation grade 4*).

Treatment of depressive symptoms in schizophrenia patients

Depressive symptoms may occur in all phases of schizophrenia, e.g., prodromal phase, first-episode, during the early course and after remission. Depression may contribute to the residual symptoms of schizophrenia. The proportion of patients with schizophrenia who also manifest depression ranges from 7 to 75% (Siris et al. 2000). Depressive symptoms have to be distinguished from side effects of antipsychotic medications (including medication-induced dysphoria, akinesia and akathisia), and the primary negative symptoms of schizophrenia (Carpenter et al. 1985, Lehman et al. 2004).

A small and modest beneficial effect of antipsychotic medication in the treatment of depressive symptoms can be assumed (*Category of Evidence B, Recommendation grade 3*). A predominant use of SGAs can be recommended with limited evidence (Leucht et al. 2009) (*Category of Evidence C, Recommendation grade 4*)

Treatment of agitation

Schizophrenic patients show agitated, aggressive or violent behavior, mostly related to psychotic symptoms (e.g., persecutory delusions, mania or hallucinations), or as a result of other symptoms, such as anxiety. Factors relating to the patient's environment or the institutions involved in treatment, such as crowded wards, lack of privacy and long waiting times, contribute to the occurrence of aggressive behavior. The prediction of aggressive and violent behavior during hospitalization is difficult; however, an association with hostility and thought disorders was reported. Physicians and staff confronted with an acutely ill, aggressive patient with schizophrenia should provide an adequate environment, reduce stimulation, try to verbally reassure and calm the person, and to deescalate the situation at the earliest opportunity (Osser & Sigadel 2001). Emergency management of violence in schizophrenia may include sedation, and, as the last option, restraint and seclusion. The use of drugs to control disturbed behavior (rapid tranquillization) is often seen as a last option, where appropriate psychological and behavioral approaches have failed or are inappropriate. The aim of drug treatment in such circumstancesis is to calm the person, and reduce the risk of violence and harm, rather than treat the underlying psychiatric condition. Psychiatrists, and the multidisciplinary team, who use rapid tranquillization should be trained in the assessment and management of service users specifically in this context: this should include assessing and managing the risks of drugs (benzodiazepines and antipsychotics), using and maintaining the techniques and equipment needed for cardiopulmonary resuscitation, and prescribing within therapeutic limits (DGPPN 2006, Lehman et al. 2004, NICE 2002). If possible, oral administration of medications is preferable to parenteral administration.

The lowest effective dose should be given, and, if necessary, gradually increased. Lorazepam and FGAs showed comparable efficacy in the acute treatment of aggression and psychomotor agitation *(Category of evidence C, Recommendation grade 4)*. Administration of low-potency antipsychotic agents, such as chlorprothixene or levopromazine, is not recommended in the treatment of agitation and excitation due to inferior efficacy or inferior tolerability *(Category of evidence C, Recommendation grade 4)*. In patients whose aggressive behavior is clearly due to psychotic symptoms, a combination treatment of lorazepam with an antipsychotic agent can be undertaken *(Category of evidence C, Recommendation grade 4)*, whereas increased side effects have to be taken into account. In general the evidence of adding benzodiazepines to an antipsychotic treatment is inconclusive. Intramuscular SGA preparations (aripiprazole, olanzapine, ziprasidone) are not inferior to intramuscular haloperidol *(Category of evidence A, Recommendation grade 1)*, but do induce less motor side effects *(Category of evidence A, Recommendation grade 1)*. However, other side effects need to be considered using intramuscular SGAs (cardiac side effects, acute metabolic side effects and others). There is a risk of sudden death following intramuscular application of olanzapine and benzodiazepines, therefore their combined use should be avoided. The combination of intramuscular benzodiazepine with clozapine is associated with respiratory failure and has to be avoided. New formulations (e.g., inhaled loxapine) are being developed and might be a promising noninvasive treatment option in future.

Measures such as restraint and seclusion should only be used in exceptional emergency situations. They should be carefully documented and explained to the patient. In all cases, the patient should be allowed to express his or her opinions and discuss his or her experience. The physician should see a secluded or restrained patient as frequently as needed to monitor any changes in the patient's physical or mental status and to comply with local law.

Catatonia

Benzodiazepines should be the first-line treatment for catatonia *(Category of Evidence C)*. ECT should be considered when rapid resolution is necessary (e.g., malignant catatonia) or when an initial lorazepam trial has failed *(Category of Evidence C, Recommendation grade 4)*.

TREATMENT-RESISTANT SCHIZOPHRENIA

Treatment resistance in schizophrenia can be defined as a situation in which a significant improvement of psychopathology and/or other target symptoms has not been demonstrated despite treatment with two different antipsychotics from at least two different chemical classes (at least one should be an atypical

antipsychotic) in the previous five years at the recommended antipsychotic dosages for a treatment period of at least 2–8 weeks per drug (Kane et al. 1988, Lehman et al. 2004, McIlwain et al. 2011, NICE 2002, 2010). Depending upon the definition of treatment resistant schizophrenia, about 10–30% of patients have little or no response to antipsychotic medications, and up to an additional 30% of patients have partial responses to treatment, meaning that they exhibit improvement in psychopathology but continue to have mild to severe residual hallucinations or delusions (Brenner et al. 1990). Even if a patient's positive symptoms remit with antipsychotic treatment, other residual symptoms, including negative symptoms and cognitive impairment, often persist. Treatment resistance is often associated with long periods of hospitalization. However, chronic hospitalization may also occur in the presence of less severe psychotic symptoms and it is not a reliable indicator of poor response to antipsychotics. The use of widespread criteria for treatment-resistant schizophrenia, including functional ones, has led to a prevalence of 55–65% following treatment with SGAs, a figure which would probably be even higher if cognitive deficits and poor quality of life were also included (Hegarty et al. 1994). Non-adherence to antipsychotic treatment remains the main cause of treatment-resistance (Goff et al. 2010). Substance abuse may also cause or, at least, contribute to treatment resistance. Nevertheless, treatment resistant schizophrenia may be associated with neurobiological factors (e.g., morphological brain abnormalities), may depend on environmental factors (e.g., unfavourable familial atmosphere, family with a high level of expressed emotions) or pharmacodynamic reasons. Multidimensional evaluation of treatment-resistant schizophrenia should consider persistent positive or negative symptoms, cognitive dysfunction with severe impairment, bizarre behavior, recurrent affective symptoms and suicidal behavior, deficits in social functioning and a poor quality of life. Therefore, in suspected treatment-resistant schizophrenia, the target symptoms should be precisely defined. Compliance should be ensured, if necessary by checking drug concentrations.

Meta-analyses from many clinical trials and reviews indicate that, in terms of efficacy, FGAs are interchangeable and that changing from an initially unsuccessful FGA to another FGA resulted in fewer than 5% of the patients achieving a satisfying therapeutic response (Conley & Kelly 2001, Kinon et al. 1993) *(Category of Evidence A, Recommendation grade 1)*. Doses higher than 400 CPZ (blocking of 80–90% of D2 receptors) do not lead to more efficacy in treatment-resistant schizophrenia, but do cause more side effects, with an emphasis on extrapyramidal motor symptoms (Kane 1994). A switch from an initially unsuccessful FGA to an SGA should instead be taken into consideration *(Category of Evidence B, Recommendation grade 3)*. Dose escalation, unless side effects

lead to an earlier drug switching, was previously recommended by an expert consensus statement (Kane et al. 2003), but recent studies do not support this statement. SGAs, especially clozapine, were discussed to be more effective in the management of treatment resistant schizophrenia than FGAs (Kane et al. 1988). Indeed, in patients with a diagnosed treatment-resistant schizophrenia according to recent definitions, clozapine should be considered as first-line treatment (*Category of Evidence B, Recommendation grade 3*). Depending on the national regulations, patients treated with clozapine should be monitored frequently with regard to hematological side effects/EEG-alterations/cardiac side effects, and a dosage range of 100–900 mg or a blood level of more than 350 ng/ml should be aimed for (*Category of Evidence B/C, Recommendation grades 3/4*) (Buchanan et al. 2010, Falkai et al. 2005). In cases of clozapine intolerance, a switch to another SGA, preferentially olanzapine or risperidone, should be performed (*Category of Evidence B, Recommendation grade 3*).

There is limited evidence for the general efficacy of ECT in treatment-resistant schizophrenia *(Category of Evidence D, Recommendation grade 5)* except for catatonia where ECT is an important therapeutic alternative (*Category of Evidence C, Recommendation grade 4*).

Apart from these treatment strategies, special psychotherapeutic (especially cognitive behavioral therapy) and psychosocial interventions to enhance the therapeutic alliance (e.g., adherence therapy, psycho-education and family interventions) and the use of long-acting depot antipsychotics should be taken into consideration.

COMBINING ANTIPSYCHOTICS

In general, antipsychotic monotherapy should be the first-line treatment in schizophrenia and the combination of antipsychotics should be a strategy for treatment-resistant schizophrenia (Barnes & Paton 2011). However, the combination of two or more anti-psychotics in clinical practice is a frequently observed phenomenon (10–50%) (Barnes & Paton 2011, Freudenreich & Goff 2002) and this trend towards polypharmacy in schizophrenia patients is increasing (Ganguly et al. 2004, Paton et al. 2008). Furthermore, other neuroactive drugs, like antidepressants, anxiolytics and sedatives/hypnotics, are commonly used concomitantly during an antipsychotic treatment (11-15%). One European study indicates that cyamemazine is prescribed up to 7.1% concomitantly to other antipsychotics (Broekema et al. 2007). However, we were not able to detect open studies or RCTs investigating this combination strategy in schizophrenia patients (*Category of Evidence C, Recommendation grade 4*).

Long-acting injectables are discussed to be a monotherapeutic alternative to oral medication, but one study shows that almost half of the patients receiving long-acting injectables are concomitantly treated with oral antipsychotics (Aggarwal et al. 2012).

REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (rTMS)

Due to the good side effect profile of rTMS, a treatment attempt with low-frequency (1 Hz) rTMS over the left temporoparietal cortex in persistent auditory hallucinations can be recommended with limited evidence (*Category of Evidence C/D, Recommendation grades 4/5*) (Aleman et al. 2007).

There is also some limited evidence for the efficacy of high-frequency rTMS (preferentially 10 Hz) to the DLPFC for the treatment of negative symptoms (*Category of Evidence D, Recommendation grade 5*) (Cordes et al. 2009).

However, there is the need for future investigations, especially to evaluate the intensity and duration of treatment and the need for a maintenance treatment.

CONCLUSION

Both FGAs and SGAs are effective in the acute treatment of schizophrenia and in relapse prevention. Clinicians must keep in mind that most patients are likely to require long-term, if not life-long, treatment which determines treatment strategy with an optimal balance between efficacy, side effects and compliance. In this regards, SGAs do have some advantages, but the risk of metabolic syndrome must be taken into account and carefully checked at regular intervals during the follow-up.

The second part of the WFSBP guidelines (Hasan et al. 2013) covers long-term treatment (dosage, duration, treatment strategies, long acting depot medication versus short acting treatment) as well as the management of relevant side effects.

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Appendix 1. Categories of evidence and recommendation grades according to Bandelow et al. (2008)

Category of Evidence description

A Full Evidence from Controlled Studies is based on:

2 or more double-blind, parallel-group, randomized controlled studies (RCTs) showing superiority to placebo (or in the case of psychotherapy studies, superiority to a "psychological placebo" in a study with adequate blinding) and 1 or more positive RCT showing superiority to or equivalent efficacy compared with established comparator treatment in a three-arm study with placebo control or in a well-powered non-inferiority trial (only required if such a standard treatment exists). In the case of existing negative studies (studies showing non-superiority to placebo or inferiority to comparator treatment), these must be outweighed by at least 2 more positive studies or a meta-analysis of all available studies showing superiority to placebo and noninferiority to an established comparator treatment. Studies must fulfill established methodological standards. The decision is based on the primary efficacy measure.

B Limited Positive Evidence from Controlled Studies is based on:

1 or more RCTs showing superiority to placebo (or in the case of psychotherapy studies, superiority to a "psychological placebo") or a randomized controlled comparison with a standard treatment without placebo control with a sample size sufficient for a non-inferiority trial and no negative studies exist.

C Evidence from Uncontrolled Studies or Case Reports/Expert Opinion

C1 Uncontrolled Studies. Evidence is based on:

1 or more positive naturalistic open studies (with a minimum of 5 evaluable patients) or a comparison with a reference drug with a sample size insufficient for a non-inferiority trial and no negative controlled studies exist.

C2 Case Reports. Evidence is based on:

1 or more positive case reports and no negative controlled studies exist.

C3 Evidence is based on the opinion of experts in the field or clinical experience.

D Inconsistent Results

Positive RCTs are outweighed by an approximately equal number of negative studies.

E Negative Evidence

The majority of RCTs studies or exploratory studies shows non-superiority to placebo (or in the case of psychotherapy studies, superiority to a "psychological placebo") or inferiority to comparator treatment.

F Lack of Evidence

Adequate studies proving efficacy or non-efficacy are lacking.

Recommendation Grade based on:

1. Category A evidence and good risk-benefit ratio
2. Category A evidence and moderate risk-benefit ratio
3. Category B evidence
4. Category C evidence
5. Category D evidence

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