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Atypical antipsychotics in the treatment of schizophrenia

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Summary

Over the last few years atypical antipsychotics have been used increasingly in the pharmacological treatment of schizophrenia. This review provides an overview of the pharmacological and clinical characteristics of atypical antipsychotics. In particular we discuss their efficacy in treating psychotic and negative symptoms as well as treatment-refractory patients. The most important side effects as well as their possible interactions are reviewed in detail. Recommendations for the clinical use are given.

Key words: atypical antipsychotics; schizophrenia; treatment; side effects

Introduction

There is overwhelming evidence that antipsychotics are superior to placebo in the acute and long-term treatment of schizophrenia [1]. In comparison to patients who continue to receive antipsychotic treatment after an acute episode, patients on placebo treatment relapse significantly more often, have to be rehospitalised more frequently and demonstrate more psychotic symptoms upon readmission. Prophylactic treatment with a standard or slightly reduced dose provides the best protection against relapse. Low dose strategies (1/10 of the standard dose) are associated with unacceptably high relapse rates of up to 60% [2]. The so-called targeted or interval treatment (tapering of the antipsychotic once the clinical situation has stabilised, recommencing of treatment when prodromal symptoms appear) are also associated with an increased risk of relapse and cannot be recommended for the majority of patients. In addition, there is evidence that this kind of treatment may be associated with an increased incidence of tardive dyskinesia [3]. In general, depot medication is not superior to oral administration with regard to various outcome criteria [4–6]. However, patients with a history of poor compliance seem to benefit most from this route of administration [7]. In general, any antipsychotic with proven effectiveness in the acute treatment phase can be used in long-term treatment as relapse prevention. After withdrawal of antipsychotics relapse may occur even after several years of full remission in up to 75% of all cases [8, 9]. Treatment with antipsychotics has been demonstrated to reduce rates of relapses and rehospitalisations in a substantial number of patients over periods of many years. For this reason antipsychotics have to be considered an effective and inexpensive treatment of schizophrenia [10].

Problems of long-term treatment

In long-term treatment studies of schizophrenia up to one third of all patients become noncompliant with treatment during the first year [11]. There are multiple reasons for this noncompliance. Some patients may refuse treatment due to poor insight, some patients as a result of psychotic symptoms themselves [12]. There may also be factors in the environment of the patient that contribute to noncompliance. For instance, in a representative survey in Germany only 20% of the interviewees recommended antipsychotics as a treatment of schizophrenia, 40% each advised against it or took an undecided view [13]. In addition, caregivers themselves may contribute to noncompliance by poorly following internationally accepted guidelines for the pharmacological treatment of schizophrenia [14]. In other cases there may be undesired side effects, such as akathisia, dystonia, parkinsonism, tardive dyskinesia, and the consequences of an increased prolactin level all of which may limit long-term treatment with antipsychotics. Also, not all patients derive a full benefit

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from treatment with neuroleptics. A substantial number of patients will relapse despite adequate antipsychotic treatment or develop partial or full resistance to treatment with antipsychotics. Finally, it is important to consider that antipsychotics primarily reduce positive symptoms, whereas so-called negative symptoms are ameliorated only to a moderate degree or may even be exacerbated [15].

Atypical antipsychotics

The observation that effective antipsychotic treatment with classical antipsychotics was associated with extrapyramidal side effects (EPS) led to the belief that only compounds that also produced these side effects were therapeutically effective. However, the introduction of clozapine in 1973 resulted in a revision of this hypothesis since this drug showed excellent antipsychotic efficacy in the absence of extrapyramidal side effects [16]. Unfortunately, the propensity of clozapine to cause agranulocytosis led to its withdrawal in many countries or to restrictions in its use [17]. In the late 1980's a pivotal multicenter study demonstrated the superiority of clozapine over classical antipsychotics in treatment-refractory schizophrenic patients [18]. This caused a resurgence of interest in this compound. Attempts to develop clozapine-like antipsychotics that lack its risk of agranulocytosis led to the introduction of new substances for the treatment of schizophrenia. These include risperidone, olanzapine, quetiapine, ziprasidone, and amisulpride. Sertindole, on the market for only a short period, was suspended in 1999 after ventricular arrhythmias due to a prolonged QTc-interval had been associated with this drug.

Despite the heterogeneity of their pharmacological and physiological characteristics all new antipsychotics, together with clozapine, are called atypical neuroleptics or antipsychotics (other terms that have been used to refer to these antipsychotics include "second-generation" and "novel" antipsychotics; throughout this paper we will use the term "atypical antipsychotics"). In the last few years positron emission tomography (PET) studies have provided important information about their mechanisms of action. Most atypical antipsychotics have been shown to demonstrate a strong affinity for serotonin 5-HT2 receptors, but relatively weak affinity for the dopamine D2 receptor (see also below). In addition, they demonstrate a selectivity for mesolimbic over nigro-striatal regions in their effects on the dopamine system [19–28]. These features are assumed to represent important common characteristics of atypical antipsychotics and to be responsible for their reduced propensity to cause EPS. This feature is often given as the main characteristic defining atypicality. Table 1 highlights some important pharmacological and clinical characteristics of atypical antipsychotics (individual features may vary for different substances). For an excellent review of atypical antipsychotics that focuses on each drug individually the interested reader is referred to a recent publication by the Task Force of the World Psychiatric Association [29].

Table 1

Pharmacological and clinical features of atypical antipsychotics.

Lower affinity for D2 receptors (except amisulpride)
Higher affinity for 5-HT2 receptors (except amisulpride)
Effective against positive symptoms
Questionably effective against negative symptoms
Lower propensity to cause EPS
Lower propensity to cause TD
Lower prolactin increase (except amisulpride and risperidone)

Efficacy of atypical antipsychotics

Positive symptoms

Positive symptoms comprise hallucinations, delusions, thought disorders, thought insertion or withdrawal as well as some psychomotor abnormalities. In controlled studies atypical antipsychotics have demonstrated comparable or even slightly better global clinical efficacy in the acute treatment of schizophrenia compared to haloperidol, while they perform significantly better than placebo in reducing positive symptoms [30–32]. These findings hold true for first-episode as well as chronic, multi-episode patients. With regard to long-term maintenance treatment all atypicals have demonstrated a positive effect on relapse prevention in controlled trials (the only exception is quetiapine for which no controlled maintenance treatment trials have been conducted). For these reasons atypical antipsychotics are recommended as first line treatment in all phases of schizophrenia [33, 34].

Negative symptoms

The term negative symptoms refers to clinical features such as flat affect, emotional withdrawal, poverty of speech and thought, lack of drive and motivation, anhedonia, disinterest, and social withdrawal. Negative symptoms are not specific to schizophrenia and have to be differentiated pri-

marily from symptoms of depression. In the assessment of negative symptoms the differentiation between primary and secondary negative symptoms has become customary [35, 36]. Primary negative symptoms are considered those that are genuine or intrinsic to the disorder, thus long-lasting and stable over time with little variation; a hypodopaminergic state of the meso-cortical dopamine system resulting in prefrontal hypodopaminergia has been implicated in primary negative symptoms [37]. Secondary negative symptoms may present similarly, but are thought to result from positive psychotic symptoms, side effects due to antipsychotic medication (parkinsonism), depressive symptoms, and social understimulation. Thus, they tend to fluctuate and should only last as long as the underlying cause is present [38].

Initial encouraging results with clozapine [18] raised the hope that atypical antipsychotics would offer a better treatment for negative symptoms than typical agents which are considered ineffective by most clinicians. However, Leucht et al. demonstrated in a meta-analysis that even classical antipsychotics are superior to placebo in reducing negative symptoms [31]. These authors found that in studies that investigated effects on negative symptoms and used haloperidol as the comparator drug only risperidone and olanzapine proved to be superior in their effects on negative symptoms, while quetiapine did not show any advantage. Since these studies did not differentiate between primary and secondary negative symptoms no conclusions can be drawn about the effects of these drugs on primary negative symptoms. For these reasons attempts have been made to use path analyses to demonstrate effects on primary negative symptoms. In these models the effects of positive and depressive symptoms as well as extrapyramidal side effects on negative symptoms are statistically taken into account and the remaining "true" negative symptom level is used to evaluate the effect of the drug in question [39, 40]. The power of this method, however, is reduced by the fact that other factors such as social understimulation, anxiety etc. are not considered in the model. In addition, the original design of the study was not intended to address the potential effect of the investigational drug on primary negative symptoms. Two recently published studies on treatment effects on negative symptoms that differentiated between primary and secondary negative symptoms could not demonstrate any significant effects on primary negative symptoms for clozapine or olanzapine [41, 42].

However, a true ameliorative effect on primary negative symptoms may be shown by the substituted benzamide amisulpride [43–45]. Amisulpride demonstrates mesolimbic selectivity and is a pure D2/D3 antagonist possessing affinity for both pre- and postsynaptic receptors. The exact role of its D3 antagonism is not known, however. At low doses the blockade of presynaptic receptors seems to prevail. This results in increased dopamine release into the synaptic cleft and thus in an activating, pro-hedonistic effect. At higher doses (>400 mg/d) the postsynaptic antagonism starts to dominate and leads to classical neuroleptic effects. Four controlled studies in patients with primary negative symptoms using doses of amisulpride between 50 and 300 mg/d demonstrated a significantly greater decrease of negative symptoms after 6 to 26 weeks of treatment in the active treatment group than in the placebo group [43–46]. It is important to note that this improvement took place independently of any changes in depressive and psychotic symptoms or extrapyramidal side effects. In addition, no increase of positive symptoms was observed. A fifth double-blind study in elderly long-term inpatients manifesting moderate to severe negative symptoms compared amisulpride to haloperidol with both drugs given in systematically reduced dosing strategy [47]. In 18% of the amisulpride group and 27% of the haloperidol group an increase of positive symptoms necessitated a dose increase. The remainder of the patients remained stable. Negative symptoms changed little over the course of the study. Still, comparison of the drug effects demonstrated a clear, albeit not statistically significant trend in favour of amisulpride in reducing flat affect and apathy [47]. (The interested reader is referred to a recently published meta-analysis of amisulpride trials by Leucht et al. [32]).

Ziprasidone, a novel antipsychotic with a unique receptor binding profile, could possibly turn out to be effective against primary negative symptoms as well. Besides its high affinity for D2 receptors and antagonistic properties at various 5-HT receptors it also demonstrates presynaptic reuptake-inhibition of serotonin and norepinephrine comparable to antidepressants [48]. The serotonin reuptake inhibition properties of ziprasidone may be important in its effects on negative symptoms since fluvoxamine, a SSRI, has been reported to reduce such symptoms in schizophrenia [49]. Indeed, in a 1-year controlled trial in patients with chronic stable schizophrenia with only moderate levels of positive symptoms but high levels of negative symptoms ziprasidone was associated with a small, but statistically significant improvement in negative symptoms compared to placebo [50]. Even more interesting, in a head-to-head comparative controlled trial over 3 months in schizophrenic patients with predominant negative symptoms ziprasidone (40–80 mg) and amisulpride (50–100 mg) demonstrated comparable efficacy in improving negative symptoms [51]. Consistently, in a 28-week comparison of ziprasidone and haloperidol in stable schizophrenic outpatients significantly more patients treated with ziprasidone demonstrated a reduction of negative symptoms of 20% or more than patients treated with haloperidol [52].

Treatment-refractory patients

Although there is no universally accepted definition of treatment refractoriness a partial or full

resistance to treatment is customarily assumed if a patient fails to adequately respond, ie, show reduction of his/her positive symptoms, to at least two antipsychotics belonging to a different chemical class given in sufficiently high doses of 6–8 weeks. An insufficient or complete lack of response to antipsychotic treatment has to be expected in up to 30% of chronic patients – a number which highlights the importance of this problem for the everyday care of these patients [16]. In 1988 Kane et al. published the results of a carefully designed study in which the superiority of clozapine over chlorpromazine in the treatment of severely ill, treatment resistant inpatients was investigated [18]. The inclusion criteria were very strict and included a documented history of three previous trials of different neuroleptics to which the patient did not show a response, a five year history of consistently low functioning and, in addition, a failure to respond to a prospective 6-week open trial of haloperidol. 268 patients fulfilled these criteria and were randomised to a 6 week double-blind treatment with clozapine or chlorpromazine. Analyses included all patients who had at least one symptom rating (1 week) after enrollment in the study. 88% in the clozapine group and 87% in the chlorpromazine group finished the study. 30% of the patients in the clozapine group met the a priori response criteria, whereas only 4% in the chlorpromazine group did so ($p < 0.001$; NNT = 4). Later studies confirmed these findings in less ill patient populations [53, 54]. Thus, the superiority of clozapine over conventional antipsychotics in the treatment of treatment refractory patients with schizophrenia is well established [30, 55].

Clozapine is the only atypical antipsychotic for which therapeutic serum levels have been established [56, 57]. Several studies have demonstrated a significantly higher response rate in patients with a serum clozapine level above 250 ng/ml (when clozapine is given twice daily) [56]. In patients who do not respond to adequate doses of clozapine (300–600 mg/d) determination of serum levels are recommended since up to 40-fold differences in serum level between patients treated with the same dose of clozapine have been described [57]. Similarly, in patients who exhibit high levels of side effects at low doses of clozapine, determination of serum levels may be informative. In addition, optimal therapeutic serum levels may also exist for olanzapine: The optimal range of olanzapine serum levels seems to be 20 to 40 ng/ml, concentrations of 80 ng/ml are associated with more extrapyramidal side effects [58].

The observation that most atypical antipsychotics share some pharmacological and clinical characteristics of clozapine has led to the assumption and expectation that they should also show superiority over classical neuroleptics in the treatment of refractory patients. A few studies seem to support this view [59–63]. However, some aspects of these studies restrict the inferences that can be safely drawn from their results. For instance, some studies used an open treatment design, in others the definition of treatment resistance was less strict; some studies also included other diagnostic groups (eg, schizophreniform or schizoaffective disorder). For instance, Bondolfi et al. [61] found response rates of 65% and 67%, respectively, in a study comparing clozapine and risperidone in 86 hospitalised patients with chronic treatment-refractory schizophrenia. These surprisingly high response rates are likely explained by the less stringent definitions of treatment resistance used in this study. In addition, patients were enrolled into the study whose lack of response was due to intolerance rather than true treatment resistance. In another controlled study with more stringent inclusion criteria concerning treatment resistance risperidone was associated with a more rapid onset of effects compared to haloperidol after four weeks [64]. However, this significant advantage in the reduction of psychotic symptoms disappeared after another four weeks. At the end of the two months study risperidone did not show any superiority over haloperidol anymore. Of particular interest is an eight week study conducted by Conley at al. [65]. This study used the almost identical study design of the seminal study by Kane et al. [18] and compared olanzapine to chlorpromazine. Treatment with neither drug was associated with a significant reduction of psychotic symptoms in these treatment refractory patients. Interestingly, the patients in this study who failed to respond to olanzapine were offered to enter an 8 week open-label treatment study with clozapine. Of the 27 patients who entered this study 11 (41%) showed a clinical response [66]. Finally, an 8 week study of quetiapine failed to show any superiority over haloperidol in the treatment of patients with a history of partial non-response to treatment with a conventional antipsychotic (fluphenazine) [67]. To our knowledge no data on the effects of amisulpride and ziprasidone in treatment-refractory patients are available at this time. In summary, superiority over conventional antipsychotics in the treatment of treatment-refractory patients has only been shown unequivocally for clozapine. Table 2 provides information about the recommended daily doses for the atypical antipsychotics discussed.

Table 2

Commonly used daily doses of atypical antipsychotics [29].[1, 2]

Risperidone	2–8 mg
Olanzapine	5–20 mg
Quetiapine	150–750 mg
Ziprasidone	80–160 mg
Amisulpride	50–300 mg[3, 5] 400–800 mg[4, 5]
Clozapine	200–600 mg

[1] individual cases, particularly first episode patients and elderly patients, may require lower doses
[2] doses amongst the compounds are not necessarily equivalent
[3] in patients with predominantly or purely negative symptoms
[4] in patients with positive symptoms, start with 400 mg/d
[5] in patients with impaired renal function the dose has to be adjusted

Neurocognitive deficits

Significant neurocognitive deficits are major and enduring features of the clinical phenotype of schizophrenia [68–71], and they impair a broad array of cognitive domains – ranging from classical neuropsychological deficits to altered information processing [72–82]. In recent years the evidence has been accumulating that they constitute a major limiting factor for rehabilitation and functional outcome [68, 72, 83].

Classical antipsychotic drugs improve these deficits only modestly at best [68, 72, 84, 85]. With the growing realisation that neurocognitive deficits constitute an important factor for the functional outcome the effects of atypical antipsychotics on cognitive deficits have been increasingly investigated. Based on the results of mostly open-label studies claims of their superiority over classical antipsychotics in this regard have been made [86, 87]. However, in a recent review of this literature and the methodology of the studies Harvey and Keefe [88] have pointed to several important factors limiting the conclusions that can be drawn from this literature: a) of a total of 20 studies reviewed only 5 employed a double-blind random assignment design and of these only 2 studies lasted more than 9 weeks whilst only one lasted more than 26 weeks; b) doses of typical antipsychotics that patients were treated with prior to being switched to atypical antipsychotics or that were used as comparator treatment were reported in only about half of the trials. When reported these doses were – based on modern standards – excessively high, ie, ranging from 736 to 924 mg chlorpromazine equivalents corresponding to about 14 to 18 mg of haloperidol. Thus, most studies were biased in favour of the atypical drug – due to the unblinded design and the unfavourable dosage of the typical agents at baseline or during the trial. Thus, many reported positive effects of atypical antipsychotics on cognition may be due to coming off an excessively high dose of typical antipsychotics. A recent study by Green et al. highlights this issue [89]. This research group had previously reported a significant improvement of verbal memory during treatment with risperidone in comparison with haloperidol given at 15 mg/d [90]. In their most recent study they compared the effects of low-dose haloperidol (mean 5 mg/d) to risperidone on cognitive deficit in a 2 year double-blind study [89]. Interestingly, they did not find any significant differences between the two treatments. Indeed, patients on haloperidol showed a more rapid initial improvement on the global measure of cognition than patients treated with risperidone. Two more recent reports on double-blind random assignment studies compared effects of haloperidol, clozapine, olanzapine, and risperidone on measures of cognition in long-tem studies [91, 92]. In the study by Purdon et al. [92] treatment with olanzapine was associated with significantly greater improvement of an index of general cognitive functioning compared to haloperidol and risperidone, whereas no difference was observed between treatment with haloperidol and risperidone. In contrast, in the study by Bilder et al. [91] both olanzapine and risperidone treatment were associated with significantly greater improvement of global neurocognitive functioning than treatment with haloperidol after 14 weeks. More detailed analyses demonstrated that the effects of the atypical antipsychotics investigated differed in the profile of their effects on different cognitive domains: While treatment with olanzapine led to improvement in the general and attentional domain, risperidone treatment was associated with significant improvement of memory functions. In addition, defining clinically significant improvement on global neurocognitive functioning as a change of at least 0.5 standard deviations the authors found that about 24% of patients treated with haloperidol, about 33% of patients treated with clozapine, about 57% of patients treated with risperidone and about 76% of patients treated with olanzapine showed clinically significant improvement – a highly significant difference. While these methodologically rigorous studies support the hypothesis of an ameliorative effect of atypical antipsychotics on cognition, caution is warranted: In the study be Purdon et al. a high drop-out rate was observed, particularly in the haloperidol group, making interpretation of the results difficult. In the study by Bilder et al. the mean doses prescribed were haloperidol 26.8 mg, risperidone 11.3 mg, olanzapine 30 mg and clozapine 498 mg. Thus, given the recent findings by Green et al., 2002, cited before, it could be argued that this study was biased against any positive findings in the haloperidol group. While true effects of atypical antipsychotics may indeed exist, the current evidence argues against an overly optimistic view until more studies using appropriate dosing of the comparator drug and employing randomised, double-blind designs have been completed. Nevertheless, given the lack of true pharmacological enhancers of cognition, atypical antipsychotics may represent the "best of all bad treatments" in clinical practice for patients with substantial cognitive deficits.

Affective symptoms and suicidality

Affective, mostly depressive symptoms, are a commonly encountered problem in the treatment of schizophrenia [93]. These may be associated with psychotic symptoms [94], but also stem from demoralisation, and from the occurrence of true major depression or the presence of a schizoaffective disorder. In general, if a patient presents with signs and symptoms of a major depression that do not remit with successful antipsychotic treatment a trial of an antidepressant drug should be initiated. However, if a patient refuses such treatment or if enduring subsyndromal affective symptoms are present, treatment with an atypical antipsychotic may offer antidepressant effects not observed during treatment with typical agents [95]. The evidence for this stems mainly from studies in patients

with schizoaffective disorder and from studies on the antipsychotic efficacy of atypical drugs in which depressive signs and symptoms were assessed as well. For a more detailed review of this topic we would like to refer the interested reader to a recently published review on this subject [95].

Suicidality represents an additional important clinical problem that unfortunately is encountered far too often in schizophrenic patients. Actual suicide attempts do not only depend on the presence of suicidality, but also on the degree of impulsiveness in a given patient – a symptom which, according to some evidence, may improve during treatment with atypical antipsychotics. Interestingly, clozapine may offer unique benefits in the treatment of suicidal patients. Meltzer et al. [96] reported on the effects of clozapine on suicidality and suicide attempts in 88 patients. These authors found a significant decrease in suicidality and in the number of suicide attempts in these patients after 6 months of treatment with clozapine compared to the period prior to clozapine treatment. These changes were associated with improvement of depression and hopelessness as well. These encouraging results were recently tested in a double-blind, random assignment, prospective study that specifically assessed the effects of clozapine and olanzapine on suicidality and suicide risk over two years [97]. A total of 980 patients were enrolled in this international, multicentre study. Clozapine significantly reduced both suicidality and suicide risk compared to olanzapine. It lowered the hazard ratio for suicide attempts significantly. Expressed differently, patients on clozapine had 24% less risk of suicide attempts or hospitalisation due to imminent suicide risk than patients on olanzapine. Thus, given the current level of evidence clozapine should be recommended as first-line treatment in patients with schizophrenia and schizoaffective disorder who are at high risk of suicidality.

Side effects of atypical antipsychotics

Atypical antipsychotics show a host of untoward effects. They can, at least partly, be understood as the result of specific antagonist action at central or peripheral receptors. In the following paragraphs the most important side effects will be discussed. For a more comprehensive discussion of all side effects interested readers are referred to the literature.

Acute extrapyramidal side effects (EPS)

Acute extrapyramidal side effects result when at least 75–80% of the D2 receptors in the basal ganglia are blocked by antipsychotics [23]. They are manifested clinically as parkinsonism, akathisia (subjective and objective restlessness) or as acute dystonia (muscle cramps in the face and neck). In contrast, particularly to high potency antipsychotics such as haloperidol that show strong and unselective affinity to the D2 receptors in the CNS, atypical antipsychotics in general cause less EPS. Therefore, their use results in a significantly lower treatment with anticholinergic medication. The available evidence indicates that clozapine and quetiapine show the most favourable EPS profile; only in very rare cases do they cause dysfunction of the extrapyramidal motor system. This is consistent with the results of several PET studies in which for both substances a subtotal blockade of 5-HT2 receptors at any dose level has been demonstrated. However, even at the highest doses D2 receptor blockade never exceeded a moderate level (about 65%) and thus remained below the threshold for the occurrence of EPS (75–80%) [21, 24, 98–100]. In contrast, the D2 receptor blockade of risperidone and olanzapine increases continuously with escalating doses resulting ultimately in EPS [21]. The threshold levels of D2 receptor blockade for the occurrence of EPS appear to be reached with a dose of risperidone of 4–5 mg/d and of olanzapine of about 20–25 mg/d [21]. When exceeding these doses a successive loss of atypical features and a significant increase in EPS has to be expected. Indeed, cases of serious akathisia have been described for olanzapine [21, 22, 101–104]. Similarly, amisulpride seems to loose its mesolimbic selectivity and to cause EPS more often when daily doses over 800–1000 mg are given [25]. Ziprasidone has demonstrated clear advantages over haloperidol in long term studies with respect to acute EPS [52].

However, individual sensitivity, rates of absorption and metabolism as well as interactions with other medications result in a substantial heterogeneity so as to make clear predictions concerning tolerance difficult.

Tardive dyskinesia (TD)

Tardive dyskinesias are those hyperkinesias that are associated with prolonged treatment with antipsychotics and manifest clinically as repetitive, involuntary, rather fast movements (smacking, blinking, grimacing, toe and finger movements), or, more rarely, as dystonic movements in various muscle groups. In contrast to acute EPS, TDs mainly emerge after a prolonged treatment with conventional antipsychotics (months to years). They are believed to be related to permanent or repeated blockade of the D2 receptors in the basal ganglia by antipsychotics. Known risk factors include higher age, affective disorders, female sex, exceeding a given cumulative neuroleptic dosage, as well as preexisting diseases of the CNS [104–106]. The emergence of acute EPS is a significant predictor for the occurrence of TD later

on [105, 107, 108]. Although the occurrence of severe TD is rather rare even mild forms can lead to social stigmatisation and reduce the compliance and acceptance of treatment. About 20–30% of all patients treated with conventional antipsychotics develop TD [105–107, 109, 110]. During the first few years of treatment the cumulative yearly incidence of de novo TD is about 5% in adult patients [111]. In elderly patients the corresponding incidence is upto 6 times higher [107, 108]. The available evidence indicates that among the newer atypical antipsychotics risperidone, olanzapine, ziprasidone, and probably also quetiapine cause less TD than classical antipsychotics [50, 112–114]. It is unclear at this point if this also holds true for amisulpride. However, an advantage, observed in an open long-term study, could not be confirmed in another controlled double-blind study in elderly chronic schizophrenic patients. After 12 months 93% in the amisulpride group and 96% in the haloperidol group demonstrated orofacial dyskinesias – which represented a small increase compared to the base-line values for both groups [47, 115]. The available evidence suggests that clozapine does not cause TD at all; up-to-date no clear case of TD that could be ascribed to the sole use of clozapine has been reported. A one year study concerning this issue could not find any evidence that clozapine can cause TD [116]. However, the available data support the notion that preexisting TD can improve during treatment with clozapine (for a review see [117]). This effect is not the result of an active process but rather due to the absence of any further noxious compounds [118]. It is also not protective since the re-exposure to classical antipsychotics will again lead to an increase of the TD rate [119].

Weight gain

In many patients treatment with antipsychotics results in a substantial, often reversible weight gain [120]. In some cases a weight gain of up to 25 kg has been observed. The mechanisms underlying this side effect are poorly understood. Factors that are thought to play a role are sedation, lack of movement, reduced satiety as well as a host of endocrinological changes [120–122]. The antagonism of central 5-HT2 receptors seems to play an important role. It is believed that this blockade results in an increased appetite and excessive food intake. This may explain why particularly atypical antipsychotics lead to substantial weight gain [123, 124]. Weight gain occurs over the whole dose range, consistent with the observation that even small doses of atypical antipsychotics result in an almost total blockade of serotonergic receptors [22, 23, 100]. After a treatment of 10 weeks the following average weight increases have to be expected: clozapine (4.45 kg), olanzapine (4.15 kg), thioridazine (3.19 kg), risperidone (2.10 kg), haloperidol (1.08 kg), fluphenazine (0.43 kg), ziprasidone (0.04 kg), placebo (–0.74 kg) [123]. Treatment with quetiapine – not included in the previously cited meta-analysis – seems to be associated with significant weight gain in some, but not all studies [124, 125]. The only exception seems to be ziprasidone – an atypical antipsychotic demonstrating presynaptic re-uptake inhibition of serotonin and noradrenalin comparable to antidepressants. Treatment with ziprasidone does not seem to induce weight gain [123, 124]. Furthermore, dyslipidaemias, particularly elevation of triglycerides, have been observed during treatment with various atypical antipsychotics [126]. It has to be stressed that such increases may occur in the absence of concomitant weight gain.

Glucose regulation

Hyperglycaemia and type 2 diabetes mellitus (DM) are more common in schizophrenic patients than in the general population. Abnormalities in glucose regulation have also been associated with the use of antipsychotic medications, especially with the use of atypical agents [127]. Though the underlying mechanism of action is not fully understood and may vary amongst different compounds there is evidence that clozapine and olanzapine induce insulin resistance leading to a pathologic glucose regulation [127, 128]. In general, weight gain is a robust risk factor for type 2 DM. In particular, being overweight at baseline, a positive personal or family history, and ethnicity (people of African descent) have found to be risk factors for developing DM during treatment with antipsychotics [127]. However, there is growing evidence that some patients treated with atypical antipsychotics may present with new onset DM or even diabetic ketoacidosis (DKA) in the absence of weight gain or any familial or individual risk factors [129]. DM or DKA have been reported repeatedly during treatment with clozapine and olanzapine and in a few single cases during treatment with risperidone and quetiapine [130–132]. For both clozapine and olanzapine the hyperglycemia resulted in at least one fatality. To our knowledge no cases of DM or DKA have been reported for amisulpride or ziprasidone.

Prolactin

Prolactin, a polypeptide of the hypophyseal gland, is tonically controlled by dopamine which inhibits by way of the portal venous system the release of this hormone. The blockade of the dopaminergic transmission results in an increase of prolactin secretion. The clinical results are dysfunction of the menstrual cycle, loss of libido, swelling of the mamillary glands as well as galactorrhea and possibly osteoporosis [133]. Due to the regionally unselective central blockade of dopamine D2 receptors all conventional antipsychotics can result in a prolactin increase. However, atypical antipsychotics vary in this regard. Clozapine, olanzapine, quetiapine, and ziprasidone result – in most cases – in a clinically insignificant or, at most, transient increase of prolactin. Risperidone does not substantially differ from conven-

tional antipsychotics in this regard. During treatment with amisulpride an even higher increase of prolactin has to be expected than during treatment with classical antipsychotics [134–138].

QTc-prolongation

QTc-prolongations have been described for all atypical antipsychotics. However, these seem to be rare occurrences with the exception of ziprasidone and sertindole which, for this reason, was suspended in 1999. According to the manufacturers specifications (as approved for Germany) ziprasidone causes a dose-dependent QTc-prolongation with an increase of 30–60 msec in 12.3% of patients. Although the information by the manufacturer does not contain recommendations for electrocardiograms (EKGs), it alerts clinicians to the possibility of QTc-prolongation. Routine EKG monitoring for ziprasidone is recommended by a recent consensus meeting [139]. For other atypical antipsychotics EKG monitoring is not routinely indicated, but should be performed when treatment with very high doses is planned or in the presence of other risk factors (eg, co-medication with possible interactions, hypokalaemia, hypomagnesaemia, cardio-vascular disease).

Other side effects

Sedation: Treatment with clozapine and olanzapine may be associated with significant sedation, whereas quetiapine and ziprasidone usually cause rather mild and transitory somnolence. On the other hand, risperidone and amisulpride can cause agitation and insomnia.

Liver enzymes: All atypical antipsychotics can lead to an increase of liver enzymes. In most cases these increases are transient without any consequences for treatment. A hepatitis proper occurs very rarely.

Agranulocytosis: Treatment with clozapine is associated with an increased risk (less than 1%) of agranulocytosis. For this reason monitoring of the white blood cell count is mandatory. Myelosuppressive effects that manifest as neutropenias or even agranulocytoses have been described for olanzapine and risperidone as well. In a few cases olanzapine prolonged neutropenias that initially occurred during treatment with clozapine [140–144].

Cholinergic system: Clozapine exerts strong anticholinergic effects centrally and peripherally resulting in problems with vision and constipation, urinary problems and – in some cases – in frank delirium. Olanzapine, quetiapine, and ziprasidone also show anticholinergic side effects, albeit to a lesser degree than observed during clozapine treatment. Risperidone and amisulpride lack anticholinergic effects. Medication with clozapine often results in sialorrhea, believed to be mediated by a direct effect on the parotid gland.

α-adrenolysis: Clozapine, risperidone, quetiapine, and – to a lesser degree – ziprasidone possess α-adrenolytic effects resulting in orthostatic hypotension and possibly reflex tachycardia. For this reason slow titration of these medications is recommended.

Sexual side effects: All atypical antipsychotics may lead to the occurrence of sexual side effects. They mainly include dysfunctions of the female cycle and of the libido as well as disorders of erection and ejaculation. These effects are believed to be mediated by drug-induced hyperprolactinemia and peripheral anti-α-adrenergic effects. It is important to address these side effects openly and directly with patients since such complaints are rarely volunteered.

Seizures: Epileptic seizures can occur occasionally during treatment with atypical antipsychotics. An increased risk is seen particularly during treatment with clozapine at higher doses (above 500 mg).

Malignant neuroleptic syndrome (MNS): The occurrence of MNS has been described for all atypical antipsychotics, even for the recently introduced ziprasidone [145]. However, the available evidence indicates that this is a rare complication, particularly in the case of clozapine. If treatment after the occurrence of MNS or malignant catatonia is indicated clozapine should be the treatment of choice since this atypical drug can be regarded as extremely safe concerning MNS [146].

Myocarditis: Myocarditis is a rare, but often fatal complication of clozapine treatment that usually occurs within the first few weeks of treatment [147,148] (see also revised package insert). In patients presenting with unexplained fatigue, chest pain, dyspnoea and other signs and symptoms of heart failure myocarditis should be considered.

Pharmacokinetic interactions

Most atypical antipsychotics are extensively metabolised by one or several of the various isoenzymes of the hepatic cytochrome P450 (CYP) system with no significant enzyme induction and no or only moderate enzyme inhibition (eg, risperidone). Caution has to be exerted when combining atypical antipsychotics with other pharmacological agents that are known to lead to induction or inhibition of liver enzymes and may thus be able to change plasma levels of medications.

Clozapine is a substrate of several CYP isoenzymes, namely CYP1A2, CYP3A4, and CYP2D6. Both ciprofloxacin (CYP1A2 inhibitor) and erythromycin (CYP3A4 inhibitor) when given together with clozapine can cause increased plasma clozapine levels and toxic symptoms such as ataxia,

dysarthria, disorientation, somnolence [149, 150]. Elevated plasma clozapine levels with or without clinical signs of intoxication are to be expected with concurrent administration of cimetidine (but not ranitidine [151]), paroxetine, fluoxetine, and caffeine. During treatment with fluvoxamine, a known inhibitor of CYP1A2, up to 10-fold increases of plasma clozapine levels have been observed [152]. A strong increase of plasma clozapine levels has been seen after the addition of risperidone to clozapine treatment, but the underlying mechanism of interaction between the two drugs remained unclear [153]. On the other hand, compounds which induce the activity of CYP450 isoenzymes (eg, rifampicin, carbamazepine) may lower the plasma clozapine levels and thus provoke a psychotic relapse. Cigarette smoking is known to induce CYP1A2 activity and smoking cessation has been related to increased plasma clozapine levels and toxic effects [154].

Risperidone is mainly oxidised by CYP2D6 and is considered itself to be a weak inhibitor of the CYP2D6 isoenzyme [153]. Co-medication with CYP2D6 inhibitors such as fluoxetine, paroxetine, perphenazine, thioridazine, and levomepromazine can lead to an increase of plasma risperidone levels, whereas carbamazepine has been linked to the opposite effect. The occurrence of parkinsonian symptoms after carbamazepine discontinuation has been reported in two patients concurrently treated with risperidone [155].

Olanzapine is mainly metabolised by the cytochrome P450 isoenzyme CYP1A2. Therefore increased plasma olanzapine levels are to be expected when CYP1A2 inhibiting compounds are co-administred, eg, fluvoxamine and ciprofloxacin. However, due to the large safety margin of olanzapine, elevated plasma olanzapine levels may lead to EPS, but rarely to other clinically relevant manifestations. Both co-medication with carbamazepine and cigarette smoking are able to decrease plasma olanzapine levels. Indeed, Zullino et al reported on a patient experiencing important extrapyramidal symptoms after reducing his tobacco consumption [154].

Quetiapine is known to be a major substrate of CYP3A4. Therefore, alterations of plasma quetiapine levels may occur when inhibitors (eg, ketoconazole, erythromycin, grapefruit juice) or inducers of the CYP3A4 isoenzyme (eg, phenytoin, carbamazepine, hypericum) are given together with quetiapine. In an open-label randomised trial co-medication with thioridazine significantly increased the clearance of quetiapine whereas haloperidol and risperidone did not have any important effects on the pharmacokinetics of quetiapine [156].

Amisulpride is metabolised less extensively by the hepatic cytochrome P450 system and its clearance occurs mostly by renal excretion. To our knowledge no important pharmacokinetic interactions concerning the cytochrome P450 system have been reported up to date and the compound my be of special interest in patients with hepatic complications due to other antipsychotics [157].

Ziprasidone is predominantly metabolised by the CYP3A4 isoenzyme and is not expected to mediate drug interactions with other coadministred CYP substrates. Hence, caution is to be exerted when CYP3A4 inhibitors or inductors (see above) are prescribed together with ziprasidone [158, 159]. Concurrent administration of carbamazepine has been reported to moderately lower plasma ziprasidone levels [158, 159].

Conclusions (see table 3)

In comparison with conventional antipsychotics atypical antipsychotics show at least an equal efficacy against positive symptoms. They may exert more beneficial effects in the reduction of global negative symptoms. The substantial advantage of atypical antipsychotics over classical compounds is the greatly reduced occurrence of acute extrapyramidal side effects and, during a prolonged treatment, a reduced incidence of TD [160]. It has to be pointed out, however, that these observations have been made in chronically ill patients and, in most cases, in comparison to rather high doses of haloperidol. For these reasons these differences may not hold true in comparison to all classical antipsychotics or in clinically different situations (for instance first episode patients). For instance, in 350 neuroleptic-naive patients treated with low doses of haloperidol (3.7 mg/d) or risperidone (3.2 mg/d) the incidence and severity of EPS was similar [161].

Atypical antipsychotics may be used in the acute and long-term treatment of schizophrenia as well as in all stages, ie, in first episode and chronic patients. However, with the exception of risperidone, soon to be marketed in an injectable slow-release formulation, none of the atypical antipsychotics is available in depot form to date; thus in many situations where compliance is crucial, classical antipsychotics in an injectable long-acting form are still the treatment of choice. In antipsychotic-naive first episode patients the lowest possible dose should be used since these patients appear to respond particularly well to antipsychotic treatments and, at the same time, are very sensitive to develop EPS [162, 163]. For instance, if sedation of a patient is required it should not be achieved by increasing the dose of the antipsychotics, but by temporarily giving an additional sedative medication such as a benzodiazepine. If negative symptoms dominate the clinical picture amisulpride in a dose of 50–300 mg/d is recommended. A concurrently existing positive sympto-

Table 3

Clinical characteristics and side effects of atypical antipsychotics.*

	Risperidone	Olanzapine	Quetiapine	Ziprasidone	Amisulpride	Clozapine
Positive symptoms	+++	+++	+++	+++	+++	+++
Primary negative symptoms1	+	+	+	++	++[2]	+
Treatment resistance	+	+	0	?	?	+++
Acute EPS	+/++[3]	0/+[3]	0	0	0/+[3]	0
TD	+	+	+	+	+	0
Weight gain	+/++	++/+++	?	0	0	+++
Prolactin increase	+/++	0/+	0/+	0/+	+++	0/+
Sedation	0/+	++	+/++	++	0	+++
Agranulocytosis	0	0	0	0	0	+
Anticholinergic effects	0/+	+	0/+	0/+	0	+++
Orthostasis (a-adrenolytic)	++	0	++	+	0	+++
Sialorrhea	0	0	0	++	0	+++
Hyperglycaemia	0/+	++	0/+	0	0	++

* the frequencies in the table are relative, not absolute and only comparable within the same row
0 not or only very rarely present
\+ rarely present, minimal effect
++ occasionally present, moderate effect
+++ often present, strong effect
[1] effects on secondary negative symptoms may be greater and clinically significant
[2] in doses of 50–300 mg/d
[3] dose dependent
? evidence not sufficient or contradictory

matology is, however, not treated with this dose. In case of a postpartal psychosis that requires antipsychotic medication women who want to breast feed their infants should not be treated with atypical antipsychotics because of the limited experience with these agents [164]. After weaning clozapine, quetiapine, olanzapine, and ziprasidone should be preferred since these substances rarely induce a sustained increase of the prolactin level. If sedative effects have to be avoided amisulpride and risperidone are recommended. The occurrence of disabling or progressive tardive dyskinesias as well as the existence of documented treatment-resistance are unequivocal indications for clozapine. A previous non-response to olanzapine is no contraindication to the use of clozapine [66]. It is always recommended to conduct changes of medication in improved or remitted patients in an overlapping fashion over days and weeks. Particular caution has to be exerted when stopping clozapine. An abrupt cessation may be associated with withdrawal symptoms, cholinergic rebounds, and, more rarely, with a very rapid emergence of psychotic symptoms (so-called rebound psychosis). In addition, cases have been described in which the superiority of clozapine was lost [165–167].

The advantages of a lower EPS liability with regard to extrapyramidal side effects contrast with some important untoward effects of atypical antipsychotics. Foremost are metabolic disorders and weight gain which have to be expected to various extent during the treatment with all atypical antipsychotics except amisulpride and ziprasidone. These side effects have to be taken seriously since they may lead to further, particularly cardiovascular, morbidity. Less dangerous, but no less disabling subjectively, are sexual side effects. However, there is evidence, particularly for clozapine, that treatment with atypical antipsychotics is associated with more patient satisfaction and may thus lead to better compliance – a crucial factor in the treatment of schizophrenia [55, 168].

Other important considerations for prescribing atypical antipsychotics are their rather high prices. If these expenses are justified – for instance by an improved long-term course of schizophrenia – remains to be seen. It is clear, however, that atypical antipsychotics should not be used irrespective of the clinical situation but tailored to the individual needs of each patient and under careful consideration of the advantages and disadvantages. Furthermore, psychopharmacological treatment of patients with schizophrenia should always be part of a sound treatment plan that includes psychosocial as well as rehabilitative interventions.

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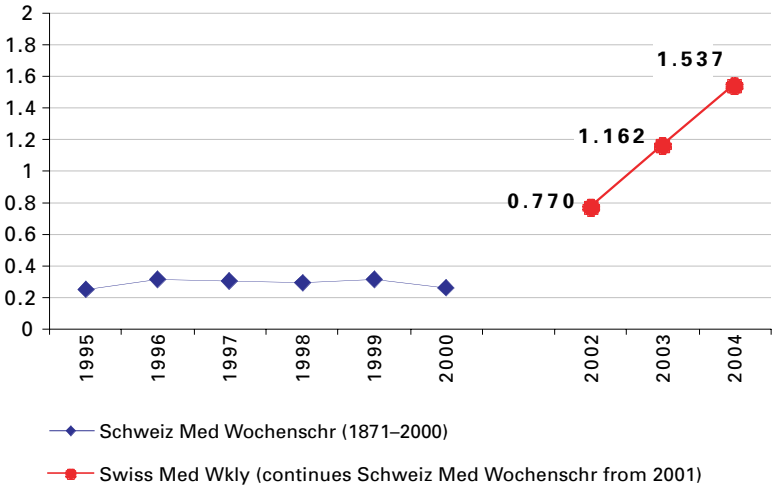

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