

Treatment Response in First-episode Schizophrenia

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First episode schizophrenia (FES) patients tend to be more responsive to treatment. An adequate response has been associated with a favourable long-term course in FES patients. Yet, despite the generally very favourable response profile around one quarter of the patients shows persisting symptoms of psychosis. To improve the outcome and course of psychosis great effort has emerged in identifying biological and clinical variables associated with non-response in order to identify non-responders as early as possible and adopt specific treatment strategies improving illness outcome. Different antipsychotic treatment regimens have been evaluated in terms of their efficacy in reducing symptoms of FES with psychological interventions gaining increasing importance in the treatment concept of patients suffering from their first illness episode. Therefore, aim of this review is to summarize current evidence on the response patterns, the most important predictors of response/non-response as well as on effective treatment interventions in FES patients.

KEY WORDS: First-episode schizophrenia; Response; Course of illness; Outcome; Predictors; Treatment interventions.

INTRODUCTION

The first episode of psychosis typically occurs during adolescence and early adulthood, a vulnerable life stage in which one deals with one's own future and personal interests including education and vocation as well as the development of relationships.^{1,2)} This contributes to the immense psychosocial and economic burden of this illness for the patient, his family and the society.³⁾ Research results have consistently shown that an adequate treatment within the early stages of psychosis is of great importance in terms of the course and outcome of the illness.^{4,5)} Today, the optimal treatment is based on the early administration of antipsychotics⁶⁾ and response to treatment within the first 1-3 months has been found to be highly predictive of subsequent partial or non-remission of symptoms.⁷⁾

It is generally accepted that first-episode patients tend to be more responsive to antipsychotic compounds compared to multiple episode patients⁸⁾ resulting in specific therapeutic recommendations for this patient subgroup in current treatment guidelines.⁹⁾ But even though most pa-

tients with first-episode psychosis respond very well to antipsychotic medication with estimates ranging as high as 87%¹⁰⁾ treatment in first-episode patients also includes patients with partial or complete non-response. A growing body of evidence underlines the importance of an early identification of non-responders to antipsychotic treatment for it could prevent unnecessary persistence with ineffectual compounds and with this reduce the duration of hospitalization, the level of care required¹¹⁾ and most important it could prevent biological and psychosocial deterioration.¹²⁾ Today, several biological and clinical predictors of early non-response have been identified and resulted in specific treatment recommendations in order to improve the outcome of the psychosis such as early intervention programs. Besides, several studies have evaluated different antipsychotic and psychosocial treatment strategies in order to identify effective and optimal treatment regimens again with the aim of ensuring a favourable long-term outcome.

On the background of the significance of an adequate and timely response to antipsychotic treatment when suffering from the first episode of psychosis, this review provides an overview on the current knowledge of response patterns in first-episode patients, and summarizes the most important predictors of response/non-response as well as the current evidence on effective treatment strategies.

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RESPONSE PATTERNS, TIME COURSE OF TREATMENT RESPONSE AND OUTCOME IN FIRST-EPISODE PATIENTS

Over the past years it has been acknowledged that response and outcome of schizophrenia vary and are heterogeneous.¹³⁾ The main challenge discussing current research evidence on response in patients suffering from their first episode of schizophrenia (FES) lies in the differing response criteria applied in the respective studies. As suggested by Leucht and Kane,¹⁴⁾ response can be defined as a clinically meaningful improvement of the patient's psychopathological symptoms irrespective of the fact whether he or she is still symptomatic. Usually, predefined cutoffs in terms of percentage reductions of the baseline score on a psychopathology rating scale are applied in order to evaluate response to treatment.¹⁴⁾ One problem is that especially in FES patients a consensus on how much improvement response really is, is still standing out. Today, the most accepted definition of response in schizophrenia research in general is a $\geq 50\%$ improvement in the respective rating scale from baseline to endpoint.¹⁵⁾ Future studies should analyse if this response criterion is also appropriate in the evaluation of FES patients. The differing response criteria applied resulting in differing study results should be kept in mind when discussing current research data on response in FES patients.

Traditionally it is believed that the course and prognosis of the patients can be roughly divided into three categories, namely in one (approximately 25% of the patients) with full response to treatment leading to a recovery from the first illness episode, in one with recurrent illnesses in form of exacerbations and remissions (around 50% of the patients) and in another group of patients with an unfavourable course and incomplete response and recovery from the first episode (25% of the patients).¹⁶⁾ The first treatment intervention in FES patients is therefore critical, for the efficacy of treatment of the first episode is associated with the prognosis of the illness.¹²⁾ A large number of randomized-controlled drug trials has shown that an adequate treatment with antipsychotic compounds is linked with a rapid improvement of psychopathological symptoms in FES patients.^{17,18)} In contrast, the specific response pattern and time course of response in FES patients has only been examined by few authors. Emsley *et al.*¹¹⁾ are among those analysing the time course of antipsychotic treatment response by examining 522 FES patients over a median treatment length of 206 days and defining response as a $\geq 20\%$ reduction in the total score of

the *Positive and Negative Syndrome Scale* (PANSS). The authors found that the time to response varied considerably with 23.3% of the patients achieving response during the first week of treatment, 23.3% at week 2, 18.5% at week 3, and 12.5% at week 4, but with 22.5% of the patients not responding until after 4 weeks and 11.5% of those patients not responding until after 8 weeks.¹¹⁾ And when evaluating the time course and biological correlates of treatment response in FES patients, Lieberman *et al.*¹⁶⁾ stated that they were surprised by the length of time required for patients to respond sufficiently and recover. In their study they examined 70 patients and identified response in 83% patients defined as a rating of mild or less in three of four positive psychotic symptom items, and an improvement of the rating on the *Clinical Global Impression Scale* (CGI) of much improved or very much improved after 6 weeks.¹⁶⁾

Although it seems as if a substantial proportion of FES patients does not improve early after receiving antipsychotics, recent research suggests that the onset of antipsychotic drug action occurs within the first 24 hours of treatment initiation.^{19,20)} However, up to today no consensus has been reached on the specific time period after which a patient should be withdrawn from the respective treatment regimen in case of non-response. Generally, treatment guidelines recommend to leave a patient on his treatment for around 4-6 weeks before evaluating response.⁹⁾ But increasing evidence has emerged that response within the first two weeks of treatment reliably predicts subsequent response suggesting that a change of treatment might be necessary already after the second treatment week in order to ensure a favourable long-term response and outcome.^{21,22)}

In this context the question arises whether limited early psychopathological improvement in FES patients is also associated with an ultimate lack of treatment response or, as suggested by the above discussed results, in FES patients it might take several weeks before a satisfying level of response is achieved. Derks *et al.*²³⁾ were among the first to explicitly examine early response to antipsychotic treatment in FES patients concurrently trying to answer the question on whether a patient should be switched to a different antipsychotic drug after 2, 4, or 6 weeks of non-response within the European First Episode Schizophrenia Trial (EUFEST). The authors were able to evaluate 299 first-episode patients over a time period of 12 months and confirmed earlier findings that the 2-week measures were associated with achieving remission after 1 year (defined following the criteria by the Remission in Schizophrenia Working Group).²³⁾ The prediction of re-

mission was found to significantly improve by the inclusion of the 4- and 6-week assessments. However, given that the prediction accuracy was only modest, Derks *et al.*²³⁾ critically question whether this leads to a clinically significant prediction. Only very recently, Gallego *et al.*²⁴⁾ reported on the time to treatment response in 112 FES patients randomly designed to olanzapine or risperidone. Response was defined as a rating of mild or better on all of the positive symptom items of the *Schedule for Affective Disorders and Schizophrenia Change Version* with psychosis and disorganization items. The authors found and estimated cumulative response rates of 39.59% by week 8 and 65.19% by week 16, but they did not find any level of percentage symptom reduction at weeks 2, 4 or 8 to be a clinically useful predictor of response by week 16.²⁴⁾ Possibly, the predictive power of early response in FES patients might depend on the assessment time point. Within our own working group and a trial performed by the Competence Network on Schizophrenia in Germany, we were able to show that when examining a short-term treatment phase (8 weeks acute treatment comparing the efficacy of risperidone and haloperidol) patients improving at least 30% in the PANSS within the first two treatment weeks could be reliably identified to be the ones achieving response ($\geq 50\%$ PANSS improvement from baseline to endpoint) and remission (defined following the criteria by the Remission in Schizophrenia Working Group) at endpoint.²⁵⁾ However, when trying to predict response one year after the patients were discharged from hospital, the psychopathological improvement beginning with week 6 of treatment was the earliest time point reliably predicting response at week 52.²⁶⁾ Taken together, current data suggest that an early response to antipsychotic treatment can be observed in FES patients and is a valid predictor of subsequent short-term outcome, however, with respect to long-term treatment a longer time period might be necessary. Therefore, treatment adaptations already within the early weeks of antipsychotic treatment seem to be critical given that response in some FES patients seem to be lagged and might result in false and unnecessary changes of treatment. Future studies are warranted to finally answer this clinically highly relevant question.

CORRELATES AND PREDICTORS OF TREATMENT RESPONSE IN FIRST-EPIISODE PATIENTS

Biological Variables

Today, advances in genetic research as well as imaging

techniques have considerably contributed to a better understanding of the pathophysiological underpinnings of response in FES patients with the latest findings summed up in this paragraph. Especially studies on never-treated first-episode patients are important in this context for antipsychotic treatment has been found to change, e.g., receptor physiology²⁷⁾ or brain morphology.²⁸⁾ Amongst others, polymorphisms in the serotonin 2A receptor or the serotonin transporter promoter gene have been associated with the clinical effect of the applied antipsychotic drugs.^{29,30)} In a pharmacogenetic study evaluating 30 variants of dopamine and serotonin candidate genes in 120 FES neuroleptic-naïve patients receiving risperidone monotherapy for 8 weeks, two SNPs in the dopamine D2 receptor and AKT1 were significant predictors of treatment response to risperidone (response defined as PANSS improvement).³¹⁾ Also, when examining polymorphisms in the D2 receptor gene in 61 FES patients and a 16-weeks treatment with either risperidone or olanzapine Lencz *et al.*³²⁾ found a significant association between the polymorphisms and response (defined as the absence of delusions, hallucinations or substantial thought disorder). However, there are also negative studies in FES and genetics such as the one by Pelayo-Teran on the catechol-O-methyltransferase (COMT) Val158Met polymorphism. This study did not find a significant association between the polymorphism and response (40% improvement in the Scale for the Assessment of Negative [SANS] and Positive Symptoms [SAPS]) in 161 FES patients assigned to either haloperidol, olanzapine or risperidone over 6 weeks of treatment.³³⁾

Imaging studies using different tools were able to identify variables significantly associated with response in FES patients. Kapur *et al.*,³⁴⁾ for example, using positron emission tomography, found a significant relationship between dopamine D2 occupancy and clinical response in 22 FES patients randomly assigned to 1.0 or 2.5 mg haloperidol with significantly increased response when the D2 occupancy exceeded 65%, 72%, and 78%. In a magnetic resonance imaging study by Szeszko *et al.*³⁵⁾ 39 FES patients were examined and randomly assigned to risperidone or olanzapine within a 16-week double-blind study defining response via psychosis and disorganization items of the *Schedule for Affective Disorders and Schizophrenia Change Version* and the improvement item of CGI. Statistical mapping results indicated that responders (25 patients) had greater cortical thickness in occipital regions and greater frontal cortical asymmetry compared to non-responders and that among the responders greater

thickness in temporal regions was furthermore associated with less time to respond.³⁵⁾

In FES patients, Garner *et al.*³⁶⁾ were furthermore able to show that larger volumes of the pituitary were significantly associated with less improvement in overall psychotic and positive symptoms measured using the *Brief Psychotic Rating Scale* in a sample of 42 drug-naïve patients treated with quetiapine over 12 weeks. In line with this result are studies postulating a significant influence of the hypothalamic-pituitary-adrenal axis and the immune system in the occurrence of psychosis, presence of clinical symptoms and response in FES patients.^{37,38)} The fact that differences in the response pattern are probably derived by the individual brain physiology are also underlined by differences in the electroencephalography (EEG) profiles comparing FES patients with an early and late response to antipsychotic treatment.³⁹⁾ Altogether, today there are several biological markers known to be associated with the patient's individual response pattern. Some of these variables, such as genetic polymorphisms or morphological brain abnormalities might serve as predictors of response in clinical routine one day allowing an individualized approach of treatment. Until then more research is needed in order to confirm present data concurrently developing strategies to implement such research results into clinical practice.

Clinical and Illness Associated Variables

Helping clinicians to identify patients in risk of non-response is believed to be a major step towards optimising therapeutic efforts, therefore in the following the factors most often discussed in the literature will be summarized. One of the variables associated with a greater likelihood of non-response to treatment is the duration of untreated psychosis (DUP). Studies provide estimates of time between the onset of symptoms of schizophrenia and the beginning of treatment varying between 22 weeks to over 150 weeks.^{40,41)} A longer DUP has been linked to a longer time to treatment response in first-episode patients and generally to an unfavourable course of the illness.^{42,43)} In one of the few long-term follow-up studies Bottlender *et al.*⁴⁴⁾ were able to show that a longer DUP was associated with more pronounced negative, positive and general psychopathological symptoms as well as a lower global functioning 15 years after the first psychiatric admission, even after effects of other factors, possibly related to the long-term outcome, were controlled for. Such findings underline the importance of establishing health service programs for early detection and treatment of FES patients

with the aim to shorten the DUP consequently improving the course and outcome of schizophrenia.

The patient's DUP has been found to be associated with the level of premorbid adjustment, a result that has led to the debate on whether or not DUP is simply an epiphenomenon of premorbid adjustment.⁴⁵⁾ Poor premorbid adjustment in turn is linked with poor response to antipsychotic treatment⁴⁶⁾ and it has been hypothesized that the poor premorbid adjustment might result in a reduced chance of detecting psychosis thus, resulting in a prolonged DUP.⁴⁷⁾ However, when analysing predictors of response in FES patients and the independent evaluation contribution of DUP and premorbid adjustment as well as age at onset, Perkins *et al.*⁴⁸⁾ were able to show that a shorter DUP and good premorbid function are independently associated with better response to antipsychotic treatment. Interestingly, both DUP and premorbid adjustment are again linked with the level of negative symptoms,⁴⁸⁾ but also positive symptoms⁴⁹⁾ with better premorbid adjustment and a shorter DUP linked to less negative and also positive symptoms. Generally, first-episode patients feature lower levels of negative symptoms compared to multiple episode patients which has been associated to a more favourable response pattern.⁸⁾ However, there are also conflicting reports from authors finding higher levels of psychopathology, including negative symptoms, to be associated with response in FES patients.⁵⁰⁾ In terms of positive symptoms there are several authors finding a higher level of positive symptoms associated with better response.^{10,46)} From a clinical point of view this result is not very surprising given that patients with acute psychotic symptoms are known to respond very well to antipsychotic treatment, whereas other dimensions of schizophrenia psychopathology seem to be less responsive.⁵¹⁾ In our own working group we analysed predictors of response in a randomized and double-blind trial comparing the efficacy of risperidone and haloperidol and also found that a higher degree of positive baseline symptoms significantly predicted achieving response ($\geq 50\%$ PANSS total score improvement from baseline to endpoint).⁵²⁾

We also found that insight into illness was a significant predictor of response namely in that sense that patients with better insight into their illness were the ones achieving response more likely compared to patients with less insight.⁵²⁾ Comparative studies are limited, however, this link between insight and response is somewhat underlined by studies in FES patients reporting that impairments in insight are a strong predictor of relapse and re-admission.⁵³⁾ In terms of treatment tolerability several authors identified

that the development of neurologic soft signs during anti-psychotic treatment was significantly associated with less likelihood of response.¹⁰⁾ And in a 1-year follow-up study Prikryl *et al.*⁵⁴⁾ examined 92 FES patients evaluating neurological soft signs using the Neurological Evaluation Scale confirming the previous research that neurological soft signs are associated with treatment response and outcome.⁵⁴⁾ The authors discuss that this association might characterize a subgroup of FES patients with a poor course of illness and outcome.

THERAPEUTIC INTERVENTIONS AND TREATMENT RESPONSE IN FIRST-EPISODE PATIENTS

Antipsychotics Treatment

As initially mentioned, FES patients differ from multiple episode patients in so far as a higher proportion of patients show a satisfying response to treatment and outcome.¹⁰⁾ Usually the antipsychotic dose required achieving response and remission is lower in FES patients⁵⁵⁾ with more susceptibility to extrapyramidal side effects in this patient subgroup.¹⁸⁾ Since the publication of the pioneering study on the efficacy of antipsychotics in FES patients in the 1970s, response rates to antipsychotic treatment have been found to be high ranging from 46 to 96%.⁵⁶⁾ With the introduction of the second generation antipsychotics, there has been an ongoing debate about a potential benefit of these compounds in the treatment of FES patients. Some evidence suggested that atypical antipsychotics affect a broader range of schizophrenia's psychopathological symptoms concurrently being better tolerated.⁵⁷⁾ Especially in terms of negative symptoms, atypical antipsychotics were reported to show superior efficacy in many of the comparator studies with typical compounds.^{58,59)}

Lieberman *et al.*⁶⁰⁾ compared the efficacy of olanzapine versus haloperidol within a randomized, double-blind trial on 263 first-episode psychosis patients finding no significant difference in terms of the baseline-to-endpoint reductions in symptom severity in the last-observation-carried-forward analyses with a follow-up of 104 weeks. However, when performing mixed-model analysis olanzapine-treated patients had significantly greater decreases in the severity of symptoms measured via the negative and general PANSS subscores and the Montgomery-Asberg-Depression Rating Scale.⁶⁰⁾ Schooler and colleagues examined 555 first-episode patients participating in a double-blind, randomized, controlled flexible-dose trial com-

paring risperidone and haloperidol with a median length of treatment of 206 days.⁶¹⁾ Authors found a significant improvement in the PANSS and CGI ratings relative to baseline with no significant differences between groups. However, they identified less relapses in the patients with clinical improvement and risperidone treatment compared to those with clinical improvement receiving haloperidol treatment.⁶¹⁾ Similarly to their results, Möller *et al.*⁶²⁾ in a double-blind randomized controlled trial were not able to observe a significant difference in the psychopathological improvements when comparing 143 FES patients receiving risperidone and 146 patients with haloperidol. Defining response based on the definition proposed by Lieberman *et al.*,⁶⁰⁾ 1) a rating of ≤ 3 in PANSS items 1-3,5,6, 2) a $\geq 30\%$ reduction from baseline in PANSS total score and 3) a CGI severity score ≤ 4 , Möller *et al.*⁶²⁾ again did not find significantly differing response rates comparing risperidone (49.3%) and haloperidol (49.6%). However, significantly fewer drop-outs and a lower prevalence of extrapyramidal symptoms were reported in the risperidone group.⁶²⁾ Within the EUFEST study Kahn *et al.*⁶³⁾ stated that symptom reduction (decrease of the PANSS total score) was virtually the same when comparing the efficacy of haloperidol, amisulpride, olanzapine, quetiapine and ziprasidone in a follow-up duration of 1 year. Again, in agreement with the previously discussed studies, Kahn *et al.*⁶³⁾ also found a higher risk for treatment discontinuation in the haloperidol group. Interestingly, when performing specific response and remission analyses within the EUFEST data, Boter *et al.*⁶⁴⁾ reported a significant difference in the response rates of the patients after one year when defining response as a $\geq 50\%$ PANSS total score improvement, with patients on a low dose of haloperidol achieving response less likely within the 12 months of treatment compared to amisulpride, olanzapine, or ziprasidone (response rates: 37% for haloperidol, 67% for amisulpride, 67% for olanzapine, 46% for quetiapine, and 56% for ziprasidone). The authors explain their differing results (no significant difference in the PANSS total score decrease but in the dichotomised response criterion) by different statistical methods applied when calculating the data.⁶⁴⁾ In a recently published review on 15 randomized controlled trials with a total of 2,522 patients no significant differences between atypical and typical drugs could be observed for the effect on symptoms or discontinuation rates,⁶⁵⁾ but atypical compounds were associated with more weight gain whereas typical compounds led to more extrapyramidal side effects so that the authors concluded that the choice of antipsychotic drug in FES

treatment is probably more influenced by the drug's side effect profile than its efficacy.⁶⁵⁾ A Cochrane review found current research basis on atypical antipsychotics for FES patients inconclusive, questioning whether the use of atypical antipsychotics would really make the treatment less off-putting and would enhance long-term compliance.⁶⁶⁾ Some results deriving from imaging studies suggest a biophysiological difference between treatment with atypical and typical antipsychotics in FES patients. Here for example Lieberman *et al.*⁶⁷⁾ found significant between-treatment differences in volume changes of magnetic resonance imaging when examining 263 FES patients treated with haloperidol or olanzapine over 104 weeks. The authors reported that haloperidol was associated with significant reductions in gray matter volume whereas olanzapine was not, questioning whether these effects could be due to haloperidol-toxicity or greater therapeutic effects of olanzapine.⁶⁷⁾ Crespo-Facorro *et al.*⁶⁸⁾ found that haloperidol, risperidone and olanzapine had equal effects in the gray matter cortical structure after 1 year of treatment in 38 drug-naïve FES patients. Besides, they reported that atypical antipsychotics had differential effects on lateral ventricle and caudate nucleus volumes. However, due to the very small sample size their results should be discussed with caution.

Taken together, a final recommendation on which antipsychotic class should be administered in order to ensure sufficient and adequate response cannot be made today. Due to the fact that on the one hand a significant benefit of treatment with atypical antipsychotics in terms of response and efficacy has not yet been proven and, on the other hand higher costs are accompanied with the treatment of atypical compounds compared to typical compounds, treatment guidelines are beginning to move away from previous recommendation of atypical antipsychotics as the first-line treatment in patients suffering from their first illness episode as performed within an update by the National Institute for Health and Clinical Excellence (NICE).⁶⁹⁾ Given that at least some of the current inconsistencies in this field might go back to methodological differences of the trials as well as to differing outcome criteria, future studies are being warranted using standardized outcome criteria in order to provide a valid knowledge basis for treatment recommendations in this patient cohort.

Despite a robust response to antipsychotic treatment in FES patients, a subgroup of patients remains with significant persisting psychotic symptoms not responding well to the first-line antipsychotic treatment applied.⁷⁰⁾ In

their review on the management of incomplete remission and treatment resistance in first-episode psychosis, Lambert *et al.*⁷⁾ provide detailed recommendations in FES patients in case of non-response conducting the pharmacological management into four stages. The authors emphasize that clinicians should carefully evaluate whether the patient has had received adequate treatment since insufficient pharmacological treatment is one of the most important confounding factors in treatment resistant assessment.⁷⁾ After combining and augmenting antipsychotic compounds (stage I and II) treatment with clozapine is recommended as stage III and augmentation of clozapine as stage IV.⁷⁾ Some authors have examined clozapine not as last treatment choice, but as first-line treatment not finding clozapine to be superior compared to comparator drugs.^{71,72)} Agid *et al.*⁷³⁾ explicitly examined how many FES patients would respond to a second antipsychotic in case of an inadequate response to the first compound and how many patients would respond to clozapine after all. The authors were able to show that in the first run 74.5% of 244 FES patients responded to antipsychotic treatment (risperidone/olanzapine) with significantly higher rates for the olanzapine-treated patients. In the second trial treatment was switched from olanzapine to risperidone or *vice versa* and performed in the non-responders of the first run. The response rate dropped dramatically to 16.6%, but was again significantly higher for olanzapine. The response rate climbed up to above 70% again in those patients with non-response that agreed to clozapine.⁷³⁾ Based on their results it is concluded that individuals should be treated with clozapine in a timely and systematic fashion in case of non-response, possibly useful already as a second-line treatment.⁷⁴⁾

Non-pharmacological Treatment Approaches

Especially in patients with insufficient response to antipsychotic treatment, non-pharmacological treatment strategies have been applied most often in order to enhance the antipsychotics' efficacy. Very recently, a case-control study on the effect of electroconvulsive therapy (ECT) in first-episode patients has been published comparing additional ECT-treatment in 74 FES patients to an allocated control group (38 patients) while they had antipsychotic treatment with survival analysis revealing that patients with additional ECT had a significantly higher cumulative response rate than controls.⁷⁵⁾ And within a naturalistic study in 7 FES patients Suzuki *et al.*⁷⁶⁾ reported of a significant improvement of the total score of the Brief Psychiatric Rating Scale (BPRS) one week after the final

session compared to the total pre-ECT BPRS score. Both studies found ECT well tolerated in FES patients and a valuable treatment option. Studies on the efficacy of other non-pharmacological strategies, e.g., transcranial magnetic stimulation in patients featuring the first episode of psychosis are still standing out.

Psychotherapeutic Approaches

Even though FES patients are generally the most responsive to antipsychotic treatment, they have been found to have difficulties accepting their diagnosis, hindering them to engage with their therapy and thus leading to treatment delay or even discontinuation of therapy.⁷⁷⁾ Early intervention programs incorporating assertive, effective and psychosocial therapy were found to enhance the therapeutic alliance, acceptance of treatment and with it the outcome of the illness. Effects on the acute response to treatment have not been in the focus of research which is why only a short summary covers this topic. Multi-element programs offer a comprehensive array of specialized in- and outpatient services supporting FES patients in problems such as engaging with the health systems or in case of substance abuse.⁷⁸⁾ Single-element interventions, mainly incorporating cognitive-behavioural therapy (CBT) as well as family interventions have evaluated the effectiveness of specific psychosocial interventions.⁷⁸⁾ Generally, only few studies evaluating CBT in FES patients are available with a reliable design and mainly only examining psychotic symptom reduction or early recovery. CBT was found to help speeding the recovery process even though no significant gains remained compared to treatment as usual at follow-up.⁷⁹⁾ Besides CBT, family interventions have aimed at reducing the adverse family atmosphere and preventing relapse or hospital admission. Such therapeutic approaches were found to vary widely with conflicting evidence in terms of the effect on symptoms, burden, social outcome or service satisfaction.⁸⁰⁾ As Crespo-Facorro *et al.*⁷⁹⁾ conclude in their update on pharmacological and psychosocial interventions, there is a great need for well-designed studies to further examine the effectiveness of CBT and family interventions in patients with a first-episode of schizophrenia, especially in terms of the acute response to treatment. Currently, optimal treatment in FES patients incorporates both psychopharmacological as well as psychosocial treatment approaches.

CONCLUSION

Response to treatment in FES patients has been found to be robust resulting in favourable response rates ranging up to 80%, yet the time course of response varies considerably. In FES patients response within the first treatment weeks was found to reliably predict subsequent response in the short-term but not in the long-term treatment. Therefore, switching strategies in case of early non-response should be carefully re-evaluated and critically discussed. Several significant predictors of response such as genetic polymorphisms and brain morphologic changes have been identified. A shorter DUP and good premorbid adjustment were among the most reliable clinical predictors of response to treatment. In terms of the most effective antipsychotic treatment strategy current study results do not give clear guidance yet. However, there are promising results of clozapine and additional electroconvulsive therapy in patients with primary non-response. Besides, early intervention strategies using psychosocial approaches such as cognitive behavioural therapy or family interventions were found to enhance the therapeutic alliance, acceptance of treatment and with it the outcome of the illness. Future research is needed in order to further examine the effects of single antipsychotic compounds. Apart from that, more research on pharmacogenetics is mandatory in order to be able to achieve personalized treatment in the future, preventing patients from ineffective compounds, reducing side effects and with this enhancing adherence to treatment and improving the outcome of schizophrenia.

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