SYSTEMATIC REVIEW

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Analysis of risk factors for antipsychotic-resistant schizophrenia in young patients – A retrospective analysis

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Abstract: *Treatment resistant schizophrenia (TRS) is a severely disabling disorder, which decreases dramatically the quality of life and overall functionality, while it increases the rate of hospital admissions and overall healthcare costs. The main objective of this research was to evaluate the risk factors for TRS in a group of patients based on a retrospective analysis. The secondary objective was to design an algorithm for initial evaluation in patients with schizophrenia, in order to detect the candidates at risk for developing TRS. Medical charts and consultation records of all patients aged between 18 and 30, diagnosed with TRS, evaluated during 1-year in our department, were selected for analysis. The most significant risk factors for TRS found in univariate model were younger age at schizophrenia onset, male gender, living in rural areas, co-morbid drug dependence, lower therapeutic adherence, and premorbid personality disorder. Marginally significant were higher Positive and Negative Syndrome Scale (PANSS) scores at previous admissions, higher scores on PANSS negative symptoms sub-scale, and lower educational background. In the multivariate model, TRS was still significantly predicted ($p<0.05$) by younger age at the disease onset, addictive co-morbidity, and lower therapeutic adherence. An algorithm based on these risk factors is suggested, based on (a) structured PANSS evaluation using SCI-PANSS and Informant Questionnaire for PANSS, (b) a scale for the detection of co-morbid drug dependence (i.e. Inventory of Drug Taking Situations, IDTS), (c) an interview for detecting premorbid personality disorders (i.e. Structured Clinical Interview for DSM IV – Axis II Disorders, SCID-II), and (d) Treatment Satisfaction Questionnaire for Medication (TSQM) for therapeutic adherence monitoring. Also, the inclusion of several pharmacogenetic parameters (at least CYP450 2D6 panel for detection of poor/ultrarapid metabolizers) could be useful when establishing an adequate therapeutic management, and may help in decreasing the rate of non-response due to variations in antipsychotics plasma levels.*

Keywords: *antipsychotics, treatment-resistant schizophrenia, pharmacogenetics, therapeutic adherence, co-morbidity*

TREATMENT-RESISTANT SCHIZOPHRENIA IN YOUNG PATIENTS – CURRENT STAGE OF RESEARCH

Young age is an important negative prognosis factor in patients diagnosed with schizophrenia, and individuals aged 26 or less at their first psychotic episode have a higher risk to be treatment-resistant [1]. This phenomenon has significant impact over patients and their caregivers functionality, but also involves higher costs for society, and especially for the healthcare system.

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Treatment resistant schizophrenia (TRS) is defined by the lack of significant clinical improvement despite therapy with two different antipsychotics from at least two different chemical classes (at least one is an atypical agent) in the previous 5 years at recommended doses for at least 2-8 weeks each drug [2]. Other definitions are more inclusive, stating that resistance is observed when the patient has inadequate response to at least two antipsychotic drugs at the maximally tolerated dose within the recommended therapeutic range in trials of at least 6 weeks [3].

Pseudo-resistance may be attributed to a large spectrum of factors, i.e. lack of therapeutic adherence, co-morbid psychiatric and/or somatic disorders, pharmacokinetic interactions, and pharmacodynamic negative impact of concomitant medication. Also, from a pragmatic perspective, cases of partial response or lack of response may be related to changes of generic antipsychotics, i.e. in patients who take different products (although with the same non-proprietary names) during successive months, due to economic or administrative issues. This observation is supported by at least a literature review which confirms clinical deterioration, adverse effects, and changes in pharmacokinetics associated with generic substitution of several psychotropics, antipsychotics included, while generics do not always lead to anticipated monetary savings and raise compliance issues [4].

To make things more complicated, certain pharmacological strategies could produce ambiguous results, i.e. combining two or more antipsychotic agents is a practice observed in more than 40% of patients with schizophrenia [5]. It's very difficult in these cases to differentiate the effect of each drug, and to monitor the clinical evolution of such patients.

A re-evaluation of the diagnosis is granted in all cases of non-response, and various psychological factors that could worsen the patient's overall status should be addressed by the case manager (i.e. housing instability or homelessness, lack of integration in the medical health system, familial conflicts). Integration of these factors in the therapeutic management of schizophrenia as possible factors for decreasing the response rate should be considered good practice.

Currently it is assumed that one third of the patients who has schizophrenia don't respond to an adequate treatment [6]. Even if these patients are switched on clozapine, after two failed trials with different antipsychotics, up to 40% of them will experience only partial remission, and full functional recovery is impossible for more than half of these individuals [7].

Various predictors for poor treatment response were reported, i.e. severity of negative symptoms, or low level of premorbid functioning [8]. Treatment-resistant patients present glutamatergic abnormalities, a lack of dopaminergic abnormalities, higher familial loading, and significant decrease in grey matter compared to responsive patients, which raises the question if a distinct type of schizophrenia could be detected from the very beggining [8]. An analysis of adult patients with TRS (N=8624) included in the Danish National Registry showed that higher rates of treatment-resistance were observed in younger individuals, living in rural or provincial areas, with lower education level, hospitalised over 30 days in the year before first schizophrenia diagnosis, who were in-patients at first schizophrenia diagnosis, with paranoid subtype, comorbid personality disorder, and/or previous suicide attempt, who used multiple psychotropic drugs (antipsychotics, antidepressants, or benzodiazepines) [9].

Pharmacogenetic studies detected associations between genes polymorphisms in pharmacokinetic (i.e. cytochrome P450 1A2 and 2D6 isoenzymes) and pharmacodynamic (i.e. D2, D4, and 5HT2A receptors) factors, and response to antipsychotics [10]. These genes are involved in various stages of processing and action of antipsychotics, from the hepatic metabolism to generation of various adverse events. If all these factors could be defined on large-scale trials, they could improve the efficacy and tolerability of antipsychotic treatment, in a future personalised medicine. Until then, several studies and case reports linked functionally 5HT3 receptors gene single-nucleotide polymorphisms (SNP) to the clozapine responsivity, and CYP1A2*1F genetic polymorphism to the clozapine metabolism [11,12]. Both these observations could explain several cases of TRS, but

larger trials are needed to confirm these reports.

A predictive model for therapeutic response in schizophrenia, based on logistic regression analyses, was suggested, and it showed that 76% of the patients carrying combination of four SNPs will have a lower response to atypical antipsychotic monotherapy [13].

Another interesting suggestion is classifying schizophrenia in different subtypes, based on biological markers, clinical staging (illness severity, prognosis, and therapeutic options), and treatment response [14]. Antipsychotic responsive schizophrenia, clozapine responsive schizophrenia, and clozapine resistant schizophrenia are the subtypes suggested by this model [14]. This classification may have important prognostic value and could help clinicians in formulating an adequate therapeutic management. Unfortunately, no good quality data exist for the next step in the treatment of clozapine-resistant patients, although co-prescribing a second atypical antipsychotic, a selective serotonin reuptake inhibitor, lithium or divalproex, glycine or D-cycloserine, and memantine has been investigated with low to moderate success [15].

Table 1. Demographic and disorder-related variables at the evaluation visit

Variables	Values	Observations
Current age	26.1 (range 18-30)	Only young patients were included in the analysis
Age at onset of the disorder	22.9 (range 18-29)	
Gender *Female* *Male*	 8 7	 53.3% 46.7%
Environment *Rural* *Urban*	 7 8	 46.7% 53.3%
Marital status *Single (including unmarried and divorced)* *Married*	 11 4	 73.3% 26.7%
Social status/income *High* *Medium* *Low*	 1 4 10	 6.7% 26.7% 66.6%
Independent living Institutionalized	14 1	This proportion could be due to the addressability of our department
Number of previous psychotic episodes	0.6 (range 0-3)	Most of the patients were at their second psychotic episode
Substance related disorders present (nicotine dependence included)	11	9%
Personality disorders present	8	53.3%
PANSS overall score PANSS-negative Scale PANSS-positive Scale	91.8 (range 86-122) 30.5 (range 15-40) 32.6 (range 20-42)	
Length of the current episode (weeks)	12.5 (range 6-30)	

OBJECTIVE AND METHODS

The main objective of this research was to evaluate the risk factors for TRS in a group of patients based on a retrospective analysis.

The secondary objective was to design an algorithm for initial evaluation in patients with schizophrenia, in order to detect the candidates at risk for developing TRS.

Medical charts and consultation records of all patients aged between 18 and 30, diagnosed with TRS,

evaluated during 1-year in our department, were selected for analysis. A number of 15 TRS cases were detected from a total of 68 patients diagnosed with schizophrenia. The diagnosis of TRS was based on DSM IV TR criteria and the World Federation of Societies of Biological Psychiatry Guidelines for Schizophrenia criteria [2].

A logistic regression analysis using SPSS 22.0 was performed on 25 demographic, clinical, and therapeutic variables, in a univariate, followed by a multivariate model. No pharmacogenetic variables could be identified in the selected medical documents.

RESULTS

The most significant risk factors for TRS in univariate model were younger onset age ($p<0.01$), male gender ($p<0.01$), living in rural areas ($p<0.05$), co-morbid drug dependence ($p<0.05$), lower therapeutic adherence ($p<0.05$), and premorbid personality disorder ($p<0.05$).

Marginally significant in the same univariate model were higher Positive and Negative Syndrome Scale (PANSS) score at previous admissions ($p=0.056$), higher score on PANSS negative symptoms scale ($p=0.058$), and lower educational background ($p=0.061$).

In the multivariate model, TRS was still significantly predicted ($p<0.05$) by younger age at onset ($p=0.022$), addictive co-morbidity ($p=0.042$), and lower therapeutic adherence ($p=0.048$).

Table 2. Risk factors for TRS in young adults

Factors	Values	
	Spearman's ρ	Linear regression p
Younger age at the current episode onset	0.467	<0.01
Gender – male	0.592	<0.01
Substance-related disorder comorbidity	0.320	<0.05
Living in rural areas	0.367	<0.05
Lower therapeutic adherence	0.322	<0.05
Premorbid personality disorder	0.298	<0.05
PANSS overall score at previous admission	0.155	0.056
PANSS-Negative Scale current score	0.152	0.058
Lower educational background	0.142	0.061

An algorithm based on these risk factors is suggested, based on:

(a) Structured PANSS evaluation based on SCI-PANSS and Informant Questionnaire for PANSS, because the previous PANSS overall scores and current Negative Scale score are correlated with the patients risk for developing TRS;

(b) A scale for the detection of co-morbid drug dependence (i.e. Inventory of Drug Taking Situations, IDTS), because current drug-related disorders should be integrated in the therapeutic management, and it has prognostic value;

(c) An interview for detecting premorbid personality disorders (i.e. Structured Clinical Interview for DSM IV – Axis II Disorders, SCID-II), because of the correlation between the risk for TRS and several premorbid disorders (especially cluster A disorders);

(d) Treatment Satisfaction Questionnaire for Medication (TSQM) for the monitorisation of therapeutic adherence, because a low therapeutic adherence is a major risk factor for developing treatment-resistance

Also, the inclusion of several pharmacogenetic parameters (at least CYP450 2D6 panel for detection of poor/ultrafast metabolizers) could be useful when establishing an adequate therapeutic management, and may help in decreasing the rate of non-response due to variations in antipsychotics plasma levels. This could have important pharmacoeconomic impact, since many antipsychotics undergo hepatic

metabolism, not to mention the risk of potential pharmacokinetic interactions between antipsychotics, or between antipsychotics and other co-administered drugs.

CONCLUSIONS

Analysis of risk factors for TRS should be included in an evaluation algorithm for all patients diagnosed with schizophrenia. While some risk factors could not be influenced therapeutically, still others can be addressed, with targeted intervention for co-morbid addictive disorders, personality disorders, negative symptoms, or with techniques for increasing therapeutic adherence.

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