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## Refractory schizophrenia: a neglected clinical problem

### Esquizofrenia refratária: um problema clínico negligenciado

Dear Editor,

Treatment refractoriness is an important and frequent problem among individuals with schizophrenia, causing enormous suffering and distress to patients and families.<sup>1,2</sup> Although psychosocial interventions are fundamental, antipsychotic treatment is the mainstay of care for schizophrenia. However, about 30% of the schizophrenic patients do not respond adequately to adequate antipsychotic treatment.<sup>2</sup> Treatment of refractory schizophrenia criteria were established based on Kane's studies with clozapine and modified by the IPAP algorithm:<sup>3</sup> 1) no period of good functioning in the previous 5 years; 2) prior non-response to at least 2 antipsychotic drugs of two different chemical classes for at least 4-6 weeks each at doses  $\geq$  400 mg equivalents of chlorpromazine or 5 mg/day of risperidone; 3) moderate to severe psychopathology, especially positive symptoms. Several studies and meta-analyses confirm clozapine's superior efficacy on treatment-refractory schizophrenia,<sup>2,3</sup> and the psychopharmacologic mechanisms involved in this superiority are not clear yet.<sup>2,4</sup> Clozapine is the best validated approach, but there are several other interesting approaches being developed.<sup>5</sup> Although refractory schizophrenia represents a challenge to the clinicians, it is often underdiagnosed and undertreated.

We have performed a study investigating the detection of the refractory schizophrenia cases in an academic outpatient clinic (Schizophrenia Program - PROESQ). We have developed a screening questionnaire describing the clinical characteristics, previous treatments and possible causes of refractoriness, and assessed 198 outpatients with diagnosis of schizophrenia and schizoaffective disorder. All psychiatrists (n = 17) were asked to point out their possibly refractory outpatients, based on four criteria stated in the questionnaire: treatment non-responder, non-compliant, clozapine user, and concomitant use of two or more antipsychotic drugs. Seventy patients (35%) met criteria for treatment refractory schizophrenia after extensive clinical chart review. Forty-seven patients (67%) were males, mean age 36 y.o. (range 17-59), the age of onset of schizophrenia was 22 y.o. (range 12-44), disease duration 13.7 years (SD = 7.8), the number of psychiatric hospitalizations was 1.8 (0 to 10, SD = 2.1), and 34.3% were alcohol and/or drug abusers/dependents. The treatment-refractory patients had used on average 4.6 (SD = 1.7) antipsychotic drugs, however only 43% (15% of all patients) had used clozapine.

These results show a low rate of recognition and appropriate treatment of refractory schizophrenia patients in an academic service in Brazil. We presume that these rates are even lower in other centers in Brazil, being a large proportion of the psychiatrists tolerant to imperative residual symptoms and misdiagnosing clinical refractoriness. Improvement on current psychiatric training is necessary to educate clinicians to recognize treatment-refractory schizophrenia and to manage the related clinical issues, such as poor compliance to medication, alcohol and drug abuse/dependence, and comorbid depression. To properly treat refractory schizophrenia patients in the public sector in Brazil, the outpatient

clinics specialized in severe mental illnesses, such as the Centers for Psychosocial Attention - *Centros de Atenção Psico-Social* (CAPS), need psychiatrists trained to prescribe clozapine and manage potentially serious adverse effects (such as neutropenia, seizures and arrhythmias) and the availability of medication and hematological exams.

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## Gene-environment interaction and violence manifestation

### Interação gene-ambiente e a manifestação da violência

Dear Editor,

It was with great interest that we read the manuscript by Mendlowicz & Figueira about intergenerational transmission of family violence, which is an important subject in times of increasing social violence.<sup>1</sup> Thus we would like to contribute to such debate, approaching the genetic participation and its interaction with environmental factors in the manifestation of this phenomenon.

Until the 80's, most researchers used to believe that abused children were more susceptible to developing violent and antisocial behaviors in the adulthood, showing the importance of environmental components as risk factors for this type of behavior. However, only in the 90's some authors started to investigate the participation of the genetic component as a susceptibility factor for the development of violent and antisocial behaviors. According to these authors, the development of violence would not only be mediated by the environment, however would be the result of the interaction between genetic and environmental factors. In the last five years, some studies have demonstrated that parental antisocial behavior prospectively predicts antisocial behavior in abused children, and that this kind of behavior presents a genetic inheritance. Antisocial violent parents are more likely to abuse their children than parents without such behavior (environmental risk for antisocial behavior in children) and also can transmit increased genetic risk for the development of antisocial behavior.<sup>2</sup>

In addition, molecular genetic studies have investigated which genes could be involved in the inheritance of antisocial violent behavior, as well as the relation between environmental and genetic factors. For example, Caspi et al. investigated a sample of 1,037 children, with 8% of them presenting history of severe maltreatment.<sup>3</sup> Such maltreated children, in an interesting way, more often carried the genotype of monoamine-oxidase type A (MAO-A) gene promoter region, which confers low levels of enzyme expression. Once carrying this low MAO-A activity genotype, the children presented a bigger chance to develop antisocial behavior. Thus, this functional polymorphism in MAO-A gene promoter region could be a risk factor for impulsive behaviors in these children. This could explain why they are more likely to expose themselves to abuse situations, and once abuse occurred, the presence of this polymorphism could contribute to the development of future antisocial traits,<sup>2</sup> demonstrating the interaction between gene-environment factors for the development of antisocial behavior. Recent meta-analysis has confirmed the association between maltreatment and antisocial behavior in individuals that present the low-MAO-A allele,<sup>4</sup> suggesting that the MAO-A gene may influence the response to environmental factors, and this biological process may be initiated early in life.<sup>4</sup> Foley et al., in a large epidemiologic twin study, described that this low-MAO-A active polymorphism was a risk factor for the development of antisocial behavior only in the presence of stressful environmental events, which isolated would not configure a risk factor for this type of behavior.<sup>5</sup> This finding confirms the importance of the interaction between genetic and environmental factors for the determination of behavioral traits.