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EDITORIAL

Here we go again! Subtyping diagnosis and refining treatments

¡Aquí vamos de nuevo! Subtipando el diagnóstico y perfeccionando los tratamientos

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New insights into the diagnosis of schizophrenia are needed to advance in the understanding of negative symptoms and the care of those individuals affected by them.[1] Primary negative symptoms are trait pathology preceding full psychosis, and those individuals with deficit schizophrenia tend to show poor clinical and functional outcome, thus early identification might turn to be crucial to establish personalized therapeutic planning.[2] Cyran and colleagues in a cross-sectional design reveal that sex (male) and low birth weight (<3,000 g) increase the risk of deficit schizophrenia, while substance abuse at psychosis onset might be more closely related to higher risk of non-deficit illness. Although the cross-sectional design of their study does not allow to make causal conclusions, its results contribute to the early identification of individuals that might present worst clinical phenotypes and progression.[3] A considerable proportion of individuals with a diagnosis of brief psychotic episode at their first episode of psychosis will develop a chronic psychotic disorder, mainly schizophrenia, where negative symptoms may be prominent.[4] In this issue, Inchausti and colleagues highlight the fact that almost 50% of brief psychosis induced by the use of substances will be diagnosed with a severe mental disorder after 16 years, with a mean time of three years until the diagnosis of a severe mental disorder is made.[5] Thus, it is well accepted that secondary negative symptoms turn out to be of substantial clinical transcendence due to its high prevalence and since they should be easier to treat than primary ones.[6]

Thanks God we have clozapine! Clozapine reduces negative symptoms significantly more than many other antipsychotic drugs and is effective also in treatment-resistant schizophrenia.[7] However, it is underutilized probably because of its side effects. Although tolerability has been found as a potential reason for clozapine discontinuation, its side effects can be detected, prevented, minimized and treated.[8] Despite of this, and unexpectedly, there is a great variability in the reporting of clozapine-related adverse events. For instance, while myocarditis is one the most serious potential side effects of clozapine, De las Cuevas and colleagues[9] identify using VigiBase, the World Health Organization's phamacovigilance database, great differences between countries in the reporting of clozapine-related myocarditis, where nearly none of the reports came from the Asian region, and half of them were from just one country, Australia. In line with this observation, Kirilochev and colleagues[10] highlight the apparent lack

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of systematic reporting of clozapine-associated myocarditis to drug agencies in Russia, emphasizing the need for increasing the efforts in reporting side effects and making clinical data available through scientific publications. However, this may be jeopardized by the flexibilization of the precautionary measures established in the past by the regulatory drug and health agencies. Stopping the compulsory reporting of the periodic hematological controls might yield a negative impact in the performance of blood controls and in the early detection of clozapine-related hematological alterations.[11] Moreover, there are certain clinical situations where these controls should be further increased. For instance, clozapine levels should be closely monitored and dose reduction may be contemplated to avoid toxicity when patients on clozapine present a systemic inflammation, either caused by an infection such as COVID-19 or due to a non-infectious cause. Interestingly, Arrojo-Romero and colleagues[12] suggest that the clozapine dosage reduction might not be necessary in every individual suffering an infection, especially in those with mild infectious symptoms and none or mild c-reactive protein elevations. Finally, in recent years new tools are being developed to facilitate the systematic evaluation of antipsychotic blood levels. With a great interest for routine clinical practice, Bernardo and colleagues[13] demonstrate the validity of Dried Blood Spot (DBP) in monitoring antipsychotics blood levels including clozapine. This new tool yields results comparable to validated, but more complex, standard laboratory technology, allowing reliable on-site examination of antipsychotic blood levels without the demanding requirements of the standard laboratory techniques, and facilitating rapid antipsychotics monitoring at clinical settings.

Here we go again, still trying to better classify our patients by understanding the relevance of negative and cognitive symptoms and their impact on outcome and functionality. It is also undoubtable that the use of clozapine warrants a more integrative view of its pros and cons leading to a complexity of clinical decisions. Thanks God we have clozapine!

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