Going Beyond “trial-and-error” in Psychiatric Treatments: OPTiMiSE-ing the Treatment of First Episode of Schizophrenia

Celso Arango1, Shitij Kapur2, and René S. Kahn*3

1Child and Adolescent Psychiatry Department, Hospital General Universitario Gregorio Marañón, IIISGM, School of Medicine, Universidad Complutense, CIBERSAM, Madrid, Spain; 2Institute of Psychiatry, Psychology and Neuroscience, King’s College London, UK; 3Department of Psychiatry, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, the Netherlands

*To whom correspondence should be addressed; Department of Psychiatry, Brain Center Rudolf Magnus, University Medical Center Utrecht, A.01.126, POB 85500, 3508 GA UTRECHT, the Netherlands. tel: 31 (0)88 755 6025, fax: 31 (0)88 755 5443, e-mail: reneskahn@gmail.com

In this issue several articles1–4 are included describing the scientific background of the Framework Program 7 (FP7) EU-funded study, Optimization of Treatment and Management of Schizophrenia in Europe (OPTiMiSE). This 6-year study is designed to develop a treatment algorithm in (first-episode) schizophrenia and the tools to predict treatment outcome and improve compliance.

While we have had effective antipsychotic treatments for nearly 60 years, the application and implementation of these treatments is far from optimal. When psychiatrists are faced with a new patient with schizophrenia they will no doubt use an antipsychotic to start treatment; however, they have little guidance on some very simple and fundamental questions. Is there a rational basis for choosing the first antipsychotic? Can I predict how well the patient will do? When the patient fails to respond adequately to their first antipsychotic how long do I wait? Do I continue for some more time, do I increase the dose or do I switch to another antipsychotic? If so, which one? Can psychosocial interventions improve compliance and outcome? And finally, when should I start considering clozapine treatment? Fortunately, first-episode patients often do respond reasonably well; the main challenge then becomes how to keep them well.

The single best predictor of continued wellness for the patient is compliance with treatment (although there is a small subgroup that eventually do well without antipsychotic drug treatment). And while every psychiatrist knows this to be the case—there are few, if any, simple, effective, and widely applicable manoeuvres at their disposal to increase compliance. OPTiMiSE addresses each of these questions in an integrative study including 500 first-episode schizophrenia patients with minimal prior exposure to antipsychotic treatment who will be followed for 1 year.

A prerequisite for the optimal treatment of schizophrenia is the ability to predict treatment outcome and the exclusion of patients whose psychotic symptoms are not due to the disorder but to underlying disorders such as substance abuse or cerebral tumor. Antipsychotic treatment in these patients is inappropriate and may delay the initiation of suitable intervention. Interestingly, despite its obvious importance, it is unknown whether a screening for organic pathology in first-episode schizophrenia makes medical and economic sense. OPTiMiSE addresses this issue by examining the clinical utility of magnetic resonance imaging (MRI) in a sample that is larger than those previously studied, and that is representative of the population of patients presenting with first-episode schizophrenia or schizophreniform psychosis across Europe.1

A second issue is whether MRI abnormalities at first presentation of schizophrenia can predict the response to subsequent treatment. Although a number of studies have reported that enlarged ventricles and reduced gray matter volume are associated with a relatively poor response, these studies have generally involved small samples in which treatment was administered naturalistically, with patients receiving a range of different types and doses of antipsychotics. Moreover, many involved chronically ill patients who had previously been treated with antipsychotics. Furthermore, most of these studies have documented statistical differences, but have not examined the positive and negative predictive value of these findings. To definitively assess the predictive value of MRI data requires a study in which previously untreated patients are scanned prior to the administration of a standard treatment, with their response assessed prospectively. OPTiMiSE collects a systematic sample of 200 with standardized, high-quality, MRI images from first-episode patients with minimal prior exposure to medication to determine if an MRI in this population has medical and clinical utility.1

Once it has been decided that antipsychotic treatment is to be initiated the question arises how to prioritize the currently available treatments in a rational and optimal
manner. Although numerous national and international treatment guidelines for schizophrenia are available, recommendations for choice of drug (or switching in case of poor response) are usually vague. A case can be made that a drug that is effective, inexpensive, widely available, and has the simplest and most specific known mechanism should be tried first. This drug is amisulpride—it is a specific D2/3 blocker, has atypical properties, is as effective as any of the other first or second generation antipsychotic medications, save clozapine, and has a relatively benign profile on metabolic parameters and in a recently completed EUFEST trial of first-episode patients showed the very best rate of remission—40% after 4 weeks of treatment. Therefore, OPTiMiSE will evaluate the application of amisulpride as the first-line treatment.

However, no one treatment will be adequate for all patients. Prospective, sequential studies are necessary to develop treatment algorithms for schizophrenia, but these are almost completely missing. The use of amisulpride as the first treatment has another benefit—it provides a rationale for the kind of drug that should be tried next. Amisulpride is a specific D2/3 blocker and thus differs from other atypical antipsychotic drugs which engage with multiple receptors. While at a group level it has been hard to show convincingly that one drug is superior to another with the exception of clozapine there may still be a rational sequential strategy. Thus, for patients who do not achieve remission on amisulpride, OPTiMiSE will compare the option of additional time on the amisulpride (the stay option) or moving to a drug that engages with multiple receptors, olanzapine. Similar to the EUFEST study, patients included in OPTiMiSE will have minimal prior exposure to antipsychotics and the issue of risk/benefit of switching from a D2/3 mechanism to a drug with a broader receptor engagement profile will be addressed.

The unfortunate reality of schizophrenia is that some patients do not respond adequately to first-line antipsychotic therapy. The treatment algorithms are quite explicit about what to do next—switch to clozapine. However, in this instance there is a huge gap between algorithms and reality. According to all treatment algorithms, if patients fail 6 weeks each for 2 antipsychotics at adequate doses they should be offered clozapine. This means that a first-episode patient should be offered clozapine within 12 weeks of start of treatment. However, standard treatment evidence shows that the average patient being initiated on clozapine has often been sick for nearly 10–12 years. Another randomized trial to demonstrate the superiority of clozapine is not needed, but early clozapine treatment needs to be tested to determine if superior outcome is achieved in first-episode patients. Thus, OPTiMiSE will provide the acceptability and outcome data on the first systematic, large-scale, application of clozapine in nonresponding patients within the first 10 weeks of their treatment initiation.

The real challenge in schizophrenia may not be inducing treatment response or even remission, but maintaining this remission. The sad fact remains that more than half of these patients will stop their medications and the majority of them will relapse over the first year. Maintaining drug treatment will substantially reduce risk of relapse and maintain clinical improvement. The challenge is how to keep these patients on the medication to which they have responded well. While a number of adherence interventions have been shown to have effect—most of them have been cumbersome, site-specific, and difficult to disseminate broadly. To be clinically relevant, we need individually tailored yet widely applicable, psychosocial interventions that incorporate elements that have been shown to be effective in previous studies. Several important elements in nonadherence can be identified: lack of insight in mental illness, negative attitude to medication, no perceived benefits, and lack of support from family members, perceived side effects and forgetfulness. To address these, OPTiMiSE has developed an IT-enabled program comprising 3 elements: web-based psychoeducation; a web-enabled personally delivered motivational intervention package; and electronic medication alerts and updates.

No 2 patients are the same. Yet, current guidelines do not address individual differences. Personalized pharmacotherapy will depend on predictors of response and drugs with different mechanisms. A critical challenge for the field (both to optimize current and to advance new treatments) is to develop predictive markers of individual differences in response profiles. Heterogeneous clinical syndromes defined by DSM/ICD diagnostic categories are inadequate for personalized therapeutics. OPTiMiSE, with its focus on patients in a similar stage of disorder and specific treatment in a standardized regimen provides the ideal background against which one can detect (biological) markers predictive of outcome. OPTiMiSE will focus on 2 broad strategies—a combination of technology-driven (pharmacogenetics, proteomics, and metabolomics) markers and hypothesis-driven (neuroimaging, neurochemical, and immune-related) markers.

OPTiMiSE will complete recruitment in early 2016. It will provide one of the largest collaborative European databases on biological markers in schizophrenia patients with little or no prior exposure to antipsychotics. The development of a treatment algorithm and identification of predictors of treatment response will have immediate and practical benefits for patients, carers, and health care professionals and prepare the field for personalized medication strategies as drugs with novel mechanisms of action become available.

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References