Effectiveness, efficiency and efficacy in the multidimensional treatment of schizophrenia: Rethinking project

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Received 10 May 2016; accepted 20 September 2016  
Available online 11 March 2017

Abstract Schizophrenia is a clinically heterogeneous syndrome affecting multiple dimensions of patients’ life. Therefore, its treatment might require a multidimensional approach that should take into account the efficacy (the ability of an intervention to get the desired result under ideal conditions), the effectiveness (the degree to which the intended effect is obtained

\hspace{1cm} \textsuperscript{*} Please cite this article as: Crespo-Facorro B, Bernardo M, Argimon JM, Arrojo M, Bravo-Ortiz MF, Cabrera-Cifuentes A, et al. Eficacia, eficiencia y efectividad en el tratamiento multidimensional de la esquizofrenia: proyecto Rethinking. Rev Psiquiatr Salud Ment (Barc). 2017;10:4–20.

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under routine clinical practice conditions or settings) and the efficiency (value of the intervention as relative to its cost to the individual or society) of any therapeutic intervention. In a first step of the process, a group of 90 national experts from different areas of health-care and with a multidimensional and multidisciplinary perspective of the disease, defined the concepts of efficacy, effectiveness and efficiency of established therapeutic interventions within 7 key dimensions of the illness: symptomatology; comorbidity; relapse and adherence; insight and subjective experience; cognition; quality of life, autonomy and functional capacity; and social inclusion and associated factors. The main conclusions and recommendations of this stage of the work are presented herein.

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Schizophrenia (schizophrenic spectrum disorders) is the most frequent psychotic disorder within non-affective psychotic syndromes, reported in DSM 5 under the heading “Schizophrenia and other psychotic disorders” and includes: schizophrenia, schizoaffective disorder, schizophreniform disorder, brief psychotic disorder, delusional disorder, substance-induced psychotic disorder, psychotic disorder secondary to a medical illness, catatonia associated with a medical illness, and unspecified psychotic disorder.

This is a clinically heterogeneous syndrome that usually affects multiple dimensions of the individual’s life, beginning frequently at the end of adolescence or early adulthood, and is associated with progressive functional deterioration in a significant percentage of cases, especially in cases where the optimal required treatment is not provided. Annual prevalence is currently 0.3% and the annual incidence is 0.8 cases per 10,000 inhabitants, which represents approximately 4000 new cases of schizophrenia diagnosed per year in Spain.1

According to the Global Burden of Disease Study in 2010, mental disorders account for 7.4% of the global burden of disease in terms of disability adjusted life years (183.9 million DALY); schizophrenia is considered to be responsible for 7.4% of that burden of disease, associated with mental disorders.2 The economic cost is a parameter that is becoming increasingly recognised in health policies and planning in research. To achieve a reduction in indirect costs, which are the majority of the costs associated with mental disorders in social, employment, family and personal terms, it should be assessed whether direct costs must be increased or not, something which is essential in the medium and long term, regardless of whether or not there is more and better social and healthcare investment in the short term to reduce the high levels of disability associated with the disease.3

The mortality rate of people with schizophrenia is twice that of the general population.4–6 The life expectancy of men and women with schizophrenia is 15 and 12 years, respectively, which is shorter than for those without schizophrenia.7

Today there is growing agreement on the influence of intensive treatments from the initial phases over the prognosis of the disease. Beyond the choice of antipsychotics for initial treatment, these intensive treatments broadly address the different needs of patients and their families.8

Early and optimal diagnosis and treatment of schizophrenia can reduce the risk of disability and increase the chances of the patient’s functional recovery. The treatment of schizophrenia requires a multidimensional approach which should take into account the following parameters: efficacy (the ability of an intervention to obtain the intended result under ideal conditions), effectiveness (the degree to which the intended effect is achieved with normal clinical practice), and efficiency (the value of the intervention with respect to the cost for the individual or society). It is in this context where evidence demonstrates the relevance
of implementing and developing optimised treatment approaches to the progression of the disease\cite{9,10} and where the Rethinking movement arises.

**Objectives and methodology**

Rethinking represents an initiative that, as its main objective, aims to draw up a number of expert recommendations on the fundamental treatment aspects of the best treatment and care in the real world for patients with schizophrenia and their caregivers. To this end, two specific objectives were proposed: 1) to assess the efficacy, effectiveness and efficiency of the treatment approaches currently adopted in our clinical environment; and 2) to identify needs which are not covered in the treatment of the disease and, therefore, propose specific action for improvement of the care and treatment of patients and caregivers. To achieve these objectives, a research methodology was designed that began with the formation of a multidisciplinary scientific committee (psychiatrists, managers, representatives of patient associations, representatives of scientific societies) from a selection of 90 recognised national experts with experience in the treatment of schizophrenia. These experts provided a multidimensional and multidisciplinary view of the disease, and committed themselves to sharing their experience in order to reach final recommendations on issues of interest.

This group of experts was selected on the basis of their professional recognition in the area of interest and the degree of experience and involvement in the treatment of those with schizophrenia in routine clinical settings. Considered and then included were professionals and groups from various different fields who were directly involved in the care and treatment of people with schizophrenia, and their caregivers: psychiatrists, psychologists, mental health nursing staff, health economics specialists, health managers, representatives of scientific societies, patient associations and patients’ relatives (Appendix A).

The scientific committee, in a first working meeting and through a reasoned group discussion, defined the overall working methodology to address the project, and posited 7 specific dimensions of the disease to work on the proposed objectives. These dimensions were as follows: symptoms; comorbidities; relapses and adherence to treatment; consciousness of illness and subjective experience; cognition; quality of life, autonomy and functional capacity, and inclusion.

The concepts of effectiveness and efficiency were specifically defined and analysed on the basis of these 7 key dimensions by the scientific committee. Working groups composed of experts from different disciplines were formed. Each working group was assigned a dimension and pairs were selected to evaluate, weight up and agree on the concepts of efficacy, effectiveness and efficiency in each dimension. In order to run this research, a critical and contrasted scientific review was undertaken to respond to the proposed topics. At a meeting where all the experts participated, the conclusions reached by each group were put together with the aim of producing a general document that would systematically record the evidence, suggestions for action and conclusions reached by the panel of experts on each of the clinical dimensions examined and analysed. The panellists, in their work, held interactive discussions, sharing their reasoned opinions and their commitment to reconsider some of these opinions by following the comments, arguments or suggestions of the other panellists in order to come to the final conclusions.

The Rethinking movement continued in a second phase in 2015, examining in greater depth the unmet needs identified by the professionals in their day-to-day work when dealing with the treatment of schizophrenia cases, and thus promote and implement areas for improvement. As a consequence of the analysis in this first part, it was considered necessary to include representatives of mental health nursing staff, due to their relevance in many of the treatment processes. The final document specifically highlights relevant and attainable intervention strategies that the experts’ group recommend by consensus, to improve the care of patients and caregivers. The results achieved were approved by the majority of the expert group, although there may have been some divergences on specific issues from a minority of the panel.

**Results**

In this article we thus present the main considerations and conclusions reached after the work done during these years by the panel of experts in order to define and describe a series of actions that would improve efficacy, efficiency and effectiveness in the current treatment of schizophrenia in our society.

**Symptoms**

Symptoms are the determinants of diagnosis and, along with functionality, the aspect that has greatest weight in the choice of treatment and in the prognosis of the patients.

Positive symptoms are of prime importance in the diagnosis of the disease\cite{12} with the most frequent being hallucinations (68%), delusions (65%) and conceptual disorganisation (50%).\cite{12} For their assessment, we have a number of validated instruments, both general (e.g., Brief Psychiatric Assessment Scale [BPRS],\cite{13} Positive and Negative Symptoms Scale for Schizophrenia [PANSS],\cite{14,15} Scale for the Assessment of Positive Symptoms [SAPS])\cite{16} as specific for different symptoms (e.g. Auditory Hallucinations Assessment Scale [PSYRATS]\cite{17,18}). The efficacy of first and second generation antipsychotics for these symptoms is similar, providing better results if good treatment compliance is assured.\cite{19} In addition to this, cognitive-behavioural therapy adapted for patients with persistent positive symptoms has been shown to be a useful intervention, although the scale of the effect observed in clinical trials is, at best, moderate.\cite{20}

It is noteworthy that in clinical practice, despite the usefulness it may have for objectifying the clinical status of patients, the routine use of these scales is minimal, their use being restricted to research environments.

At present, there is some controversy as to whether the symptoms of disorganisation (thought, language, behaviour) should be included in the positive dimension\cite{21} or, on the contrary, they should make up an independent dimension.\cite{22} From the point of view of their assessment, there are no specific psychometric instruments validated in Spanish. Their
assessment therefore falls on the items on the positive symptom scales, such as the PANSS and the SAPS, and the clinician-assessed item from the severity scale of the symptoms for the dimensions of psychosis.22

Negative symptoms are present in 58% of patients during the first episode.24 They are better predictors of progression than positive symptoms25,26 and, along with cognitive symptoms, have a major impact on functioning, lifestyle and somatic health.27 Several batteries and scales have been drawn up for assessing the psychopathology of negative symptoms, including the following scales: Brief Scale for Negative Symptoms (BNSS),28 the Interview for the Clinical Assessment of Negative Symptoms (CAINS),29,30 the Inventory for Deficient Schizophrenia Syndrome (SDS)31,32 or the Scale for the Assessment of Negative Symptoms (SANS).33,34 There are also scales such as the PANSS, which in some of their sections, measure negative symptoms, or others that assess secondary negative symptoms such as motor symptoms (e.g. with the modified Simpson-Angus Scale).35

Among the limitations we have in evaluating the efficacy of antipsychotics for these types of symptoms is the difficulty, in clinical trials, of distinguishing between primary negative symptoms—directly related to the pathophysiology of schizophrenia—and symptoms which are secondary to psychotic, affective symptomatology, concomitant diseases or the side effects of some drugs. The main reason is that the scales usually used in research and clinical settings do not have the capacity to adequately identify this symptomatology, resulting in an under- or over-inclusion of symptoms and behavioural assessment rather than experiential assessment.36 There are no drugs that have demonstrated efficacy for primary negative symptoms.26,37 Furthermore, it seems that drugs that block dopaminergic receptors, such as antipsychotics, can produce negative symptoms in healthy people.38 Although psychosocial interventions have been more studied for the management of positive symptoms, there is some evidence that cognitive-behavioural therapy, social skills training, and combined interventions are associated with continued improved negative symptoms for more than 6 months. There are, however, many questions to be clarified regarding these interventions, such as whether or not combined treatments can produce greater and more lasting improvement.39-41 There is currently no approved pharmacological approach for the treatment of primary negative symptoms, revealing a key unmet need in this area of treatment.42 The efficacy results of some new treatments aimed at increasing glutamatergic neurotransmission and associated with antipsychotics were promising in phase II, although the Phase III studies did not confirm these results.43,44 Negative symptoms secondary to positive symptoms, depressive symptoms or antipsychotic treatment, would require specific treatments.

Affective symptoms of schizophrenia have received little attention, although 25%-30% of patients present post-psychotic depression.45 Diagnosis is difficult, especially differential diagnosis with negative symptoms. For its assessment, we have the Calgary Depression Assessment Scale.46,47 Data on efficacy and efficacy of antipsychotics for these symptoms is in short supply and suggests limited efficacy, although this is probably higher for some second generation antipsychotics.48 With regard to manic symptoms, it is known that their presence contributes to the prognosis of schizophrenia. Moreover, DSM-5, in its deconstruction of the disease, includes mania in its severity scale of symptoms of psychosis dimensions, as assessed by clinicians.21 Another instrument that has been used to evaluate manic symptoms in schizophrenia is the Young Mania Rating Scale,49 although its validity for assessment in patients with schizophrenia has been little researched.50

Up to two thirds of patients with untreated schizophrenia have motor symptoms.51 Motor symptoms are also frequent in patients receiving antipsychotic treatment, with differences between different drugs.52 Several scales, such as the Simpson Angus Scale (SAS)53 the Abnormal Involuntary Movement Scale (AIMS),54 and Barnes’ Scale for Assessment of Akathisia (BARS)55 are available for assessment. There are virtually no efficacy studies to guide the treatment of these symptoms. The two most serious situations are catatonia and tardive dyskinesia. Benzodiazepines and electroconvulsive therapy can be used for catatonia.56 For tardive dyskinesia the treatment alternatives provide very limited results.

The prevalence of consummate suicide in patients with schizophrenia is 4.9%-55 and the highest proportion of suicides occur during the first 2 years from the onset of the disease.56,57 The Beck Suicide Intent Scale (BSIS)58 or the Columbia Suicide Severity Rating Scale (CSSRS) can be taken for suicide risk assessment.59 Preventive treatment for suicide risk has been little researched and currently only one pharmacological treatment, clozapine, is considered efficient and effective.60,61 Suicide risk management is also important in the treatment of comorbidities such as depression or substance use disorders.

Along with the risk of suicide, in some cases patients with schizophrenia may exhibit aggressive behaviour. It is important to note that people with psychopathologically stabilised schizophrenia do not present violent behaviour more frequently than the general population.62-64 Aggressive behaviour is more frequent prior to diagnosis and has as risk factors positive symptoms, comorbidity with substance abuse disorders, lack of adherence to treatment, recent exacerbation, vital stressors in childhood and psychopathic traits of personality.65,66 The most widely used validated assessment tool is the Manifest Aggressive Scale (OAS).67 The treatment approach will depend on the paths leading to this aggressive behaviour; If aggression is related to psychotic symptoms, clozapine is an effective treatment, but if this behaviour depends, for example, on the presence of comorbidity with a substance abuse disorder, it may require other drugs or psychosocial interventions.67 Regarding the treatment of aggressive behaviour, it is possible to indicate that both first and second generation antipsychotics are effective, and clozapine seems especially useful in the management of these patients.57

Multiple unmet needs have been detected in relation to the symptoms of schizophrenia that affect efficacy, effectiveness and efficiency. The persistence of symptoms, especially negative or cognitive symptoms, from many of these dimensions in a significant proportion of symptomatic patients after initiating treatment—or resistance to the treatment of positive symptoms—advocates the need for more effective treatments and the search for new treatment targets with different mechanisms of action.26,68,69 Cognitive-behavioural therapy may be effective for certain symptoms and can lead to a substantial reduction
in relapses; it improves the patient’s adaptation to his environment and his overall functioning, although recent meta-analyses do not demonstrate greater efficacy for this type of therapy than other less sophisticated and less demanding interventions.\textsuperscript{70,71} Thus, further studies on the effectiveness and efficiency of the combination of psychopharmacology with different psychosocial interventions are needed.

Most research on the results of pharmacological interventions in schizophrenia has focussed more on improving symptomatology (especially positive symptoms) and not on how this translates into an improvement in functionality and the quality of life of the patient. In addition, variable compliance has not received the necessary attention and this variable affects many of the symptoms assessed in the studies. More pragmatic clinical trials are needed that would respond to clinical questions that are more focussed on not only positive symptoms (the need to improve treatments for primary negative symptoms) and which would enable assessment of outcomes under real-life conditions. These studies should include cost-effectiveness measures.

Comorbidities in schizophrenia

Assuming remission and/or recovery as a treatment objective, the treatment of schizophrenia should go beyond the management of psychosis exclusively, also encompassing general health.

From the point of view of physical health, the most frequent comorbidities are those related to cardiovascular and metabolic risk factors.\textsuperscript{72-74} However, other medical co-morbidities such as oral problems, osteoporosis or pulmonary thromboembolism should be considered, to name but a few, which may also be present more frequently in these patients. Although this is associated with other comorbidities such as anxiety disorder or posttraumatic stress disorder, the most common comorbidities in patients with schizophrenia are obsessive compulsive disorder (prevalence 3.5–46%), substance abuse disorders (prevalence 47%), and depression (vital prevalence 81%).\textsuperscript{75}

Diagnosis, especially early diagnosis, of physical comorbidities continues to be an important area of improvement in the management of these patients by all involved (patient, primary care physician and psychiatrist). The “Consensus on the physical health of the patient with schizophrenia on the part of the Spanish Societies of Psychiatry and Biological Psychiatry”\textsuperscript{76} has had a very limited impact on clinical practice\textsuperscript{72}; unfortunately, this lack of follow-up of the guidelines for the management of psychotropic drugs extends to other specialties.\textsuperscript{73} Health promotion and prevention programmes require to be introduced for people with schizophrenia, and this entails greater coordination between health care networks and an assessment of their efficacy, effectiveness and efficiency, since the available information indicates a clear lack of evidence in this regard.\textsuperscript{72}

The presence of physical comorbidities in patients with mental disorders increases costs. Specifically, schizophrenia is associated with higher costs per case than depression, in part because there is a higher risk of presenting physical comorbidities.\textsuperscript{79} This is a fundamental factor that has not been taken into account when assessing not only the efficiency but also the effectiveness and efficacy of the treatments of schizophrenia.

Just as we have indicated for diagnosis, the treatment of comorbidities, whether physical or mental, in some cases requires specific interventions (for example, treatment for cannabis abuse, smoking, guidance in healthy habits) and a prospective assessment of the usefulness and value of these interventions, all with a patient-centred approach. The initial results of some pragmatic clinical trials suggest that measures of that type could be effective and cost-efficient.\textsuperscript{80}

In conclusion, the presence of comorbidities is one of the least developed fields of schizophrenia, and influences the efficacy, effectiveness and efficiency of the treatment of schizophrenia. It is therefore necessary to design education and awareness programmes for patients, primary care physicians and psychiatrists in order that all understand the importance of improving physical health, especially reducing cardiovascular and metabolic risk factors. Improving lifestyle and counteracting the side effects of treatments through specific intervention programmes are critical factors in this regard. Clinical practice and scientific evidence show the need to establish a comprehensive approach to health in patients as a way of achieving functional recovery.

Adherence to treatment and relapses

Adherence is defined as the extent to which a person’s behaviour in terms of following prescribed treatment (pharmacological treatment, psychotherapy, lifestyle changes, etc.) corresponds to recommendations agreed with a healthcare provider. Partial adherence or complete withdrawal from treatment is often common in severe mental disorders; it is estimated that approximately half of the patients with schizophrenia usually stop taking 30% or more of the prescribed medication.\textsuperscript{87,88} Lack of adherence is associated with serious clinical consequences (increased risk of relapse, suicide or aggressive behaviour, among others) and high costs, both in monetary terms and psychosocial resources.\textsuperscript{83,84}

In general, lack of adherence is of extraordinary relevance in all chronic diseases. It is estimated that between 33% and 69% of all hospital admissions in the U.S. are due to lack of adherence.\textsuperscript{85} The ability of clinicians and informal caregivers to address this problem is limited. Initiatives that improve adherence are key to progress towards more effective and comprehensive treatment plans.

Adherence assessment can be performed with direct methods, such as determining plasmatic levels of the drug or its metabolites, or indirect methods, such as medication count, patient interview or questionnaire use, although the only one validated in Spain is Morisky-Green’s.\textsuperscript{86,87} The recommendation is to use both assessment methods as they provide complementary information. The most important factors associated with lack of adherence are lack of disease awareness, lack of adherence, presence of substance abuse disorder, lack of efficacy or poor tolerability of antipsychotic treatment, lack of family support, critical attitude and stigmatisation by the family.\textsuperscript{88-90} Possible strategies to improve adherence include: 1) pharmacological strategies, selecting the drug according to its profile of adverse effects,
dosage and patient preferences, using long-acting intramuscular antipsychotics and avoiding combination therapy and 2) non-pharmacological strategies such as psychoeducation; strengthening the treatment alliance through decision-making techniques shared with the patient, and community assertive therapy, which have been shown to be efficacious, effective, and possibly efficient. In randomised clinical trials it has been observed that early intervention with family therapy reduces the severity of symptoms and improves access to treatment and compliance with it. Early intervention with cognitive-behavioural therapy reduces the severity of symptoms, with a low impact on relapses and hospital admissions.

There is no universally accepted definition of relapse. The most frequently used in the literature is hospitalisation, although many others have been used that include scores on scales, subscales or items, behavioural changes or other operational criteria such as those of Csernansky and Andreasen. Among the factors that precipitate relapse are poor adherence to treatment, environmental stress, depression, substance abuse and history of relapse, and among protective factors: good adherence to treatment, duration of untreated psychosis less than 60 days and good response to treatment.

Recent studies show the effectiveness of maintaining antipsychotic treatment with minimal effective doses for the prevention of relapses as a maintenance treatment. However, further maintenance treatment studies are required to compare with withdrawal of medication before it can be concluded that the best treatment strategy in patients with schizophrenia, following an acute psychotic episode, is indefinite maintenance treatment.

Relapses have relevant clinical and socioeconomic consequences. From the clinical point of view, it has been estimated that two-thirds of patients have a relapse and, of those who do, one in 6 does not recover from the episode. The costs of relapses, defined as hospitalisations, are high because they account for 38.5% of total costs of schizophrenia, only surpassed by the cost of informal care (47%) and well above the pharmaceutical cost (12.8%).

Insight and subjective experience

Absence of insight of illness and subjective experience is a key aspect in the prognosis of psychosis. The lack of insight into the existence of a chronic disease that needs treatment is a non-specific manifestation but is a characteristic of psychosis. This is a complex and multidimensional phenomenon that includes recognition of having a illness (what has been called cognitive insight), and awareness of clinical symptoms and the need for treatment (so-called clinical insight). Disease insight is often an indicator of state and not of trait, and is therefore a modifiable factor, which is relevant since it is an important predictor of functioning after a first psychotic episode. Subjective experiences are those related to the identification of, strictly speaking, subjective aspects of the mental states of the patient and which require the subject himself to be identified. It is necessary to distinguish between subjective experiences with taking antipsychotics, on the one hand, and subjective experiences as a vital situation, on the other, the latter being closer to the dimension of quality of life.

The assessment of both insight and subjective experience with medication will depend on the type of treatment intervention. If the objective is to assess response to medication, insight can be assessed using the Birchwood Insight Scale (IS) or the Scale to Assess Unawareness of Mental Disorders (SUMD). If the objective is the assessment of psychosocial treatment, the recommendation is to use the Beck Cognitive Insight Scale (BCIS) or the Personal Beliefs about Illness Questionnaire-revised (PBIQ-R). Similarly, for the assessment of subjective experience with treatment, the recommendation would be to use the Drug Attitude Inventory (DAI-30 or the abbreviated version DAI-10) if the objective is to assess pharmacological treatment, or the Subjective Well-Being under Neuroleptics Scale (SWN-K) to evaluate psychosocial interventions.

There are few assessable studies on the effect of antipsychotic medication on insight and with inconclusive results. With regard to psychosocial interventions, the promotion of support and social relations has been assessed, along with vocational rehabilitation, cognitive-behavioural therapy, motivational intervention therapy aimed at increasing adherence, training in social skills, and self-observation through video and comprehensive interventions. In general, these interventions have a modest effect on the modification of insight, with very heterogeneous results. On the other hand, there is still insufficient evidence to show that improved insight is associated with better health outcomes for the individual, and studies on this are required.

Cognition

In schizophrenia basically 7 domains of cognition are affected from the early stages of the disease: processing speed, attention, working memory, verbal and visual learning, reasoning and problem solving. As a consequence, the productivity of patients, their quality of life and social functioning is affected. Therefore, it is considered important to evaluate the cognitive functioning deficit in patients with schizophrenia, especially at debut, in patients with a recurrent or refractory progression, or in those who complain of amnestic discomfort or functional deterioration. There are multiple instruments for the assessment of cognitive function in patients with schizophrenia, which include complete neuropsychological batteries such as MATRICS, developed for use primarily in clinical trials, or instruments that have been validated in our setting, such as the Brief Scale to assess Cognitive Impairment In Psychiatric Patients (SCIP) or the Behavioural Assessment of the Designative Syndrome (BADS). Cognitive interview tools have also been developed, such as the Schizophrenia Cognition Rating Scale (SCoRS), which can help assess the level of cognitive impairment of the patient, and are being used in clinical trials for the assessment of interventions directed to this. However, more pragmatic tools are needed to allow screening of cognitive disorders in patients with schizophrenia.

The study of the variables that can mediate cognition, both in general cognitive functioning and social cognition, has been very limited, with small sample size in studies and...
with limitations when measuring the desired variables. So far it has only been possible to demonstrate that clinical factors and psychological treatments are mediators which are moderately related to cognition.\textsuperscript{70, 125} Thus, patients with greater severity of symptoms present poorer neurocognitive performance, this being related to poorer social functioning. This last is influenced by the duration of unmasked psychosis\textsuperscript{126}. Both cognitive therapy in the case of neurocognition, and intervention programmes on social cognition are the programmes that have yielded the most promising results to date.\textsuperscript{127}

As with primary negative symptoms, most studies evaluating the efficacy of antipsychotic drugs to improve cognition in schizophrenia, when taking into account improvement, secondary to a reduction in positive symptomatology, do not find positive results in this domain.\textsuperscript{128} Moreover, in both animal models and healthy individuals, dopaminergic receptor blockers appear to worsen cognitive performance.\textsuperscript{129} Given the limitations of pharmacological treatments, neuropsychological rehabilitation therapies encompassed within the term “cognitive rehabilitation techniques” (CRT)\textsuperscript{130} have been proposed as an adjunctive treatment for cognitive disorders. They consist of applying specific techniques directed at exercising cognitive abilities and learning compensatory strategies, directed and supervised by a therapist.

There are different formats and programmes that can be presented in traditional pen and paper format or through computer programmes.\textsuperscript{132} The objective of the CRTs is to alter the level of individual functioning by improving the deficient cognitive area. For a CRT to be considered effective, it should be generalised to daily life. Overall, we can say that cognitive rehabilitation can become the critical factor for treatment success in at least one group of patients. It is important to note, in this regard, that cognitive impairment is present in the early stages of the disease and that cognitive rehabilitation shows moderate to major changes in these stages.\textsuperscript{131} The use of new technologies for cognitive training has succeeded in influencing the facilitation of mechanisms of cerebral plasticity\textsuperscript{32} and at the same time promoting improvements in functioning in the real world.\textsuperscript{133}

In summary, clinicians should be aware that cognition is affected in most patients, even before the onset of the disease, and is therefore an important part of the clinical assessment of patients. It should be noted that alterations in cognition are associated with a greater degree of functional and social disability. This association has made cognition a relevant treatment target. The investigation of treatment strategies aimed at improving cognition is still at a very early stage, and there is still no suitable pharmacological treatment. Although this is an area that needs further development, cognitive rehabilitation is the most interesting option.

**Quality of life, autonomy and functional capacity**

The approach to treatment of people with schizophrenia requires a paradigm shift, which would lead to a greater degree of personal recovery, attempting to restore the premorbid situation and resume daily life.\textsuperscript{134} This implies focussing on three fundamental aspects: quality of life, personal autonomy and social functioning. Quality of life, as a subjective assessment of the person’s life circumstances; personal autonomy, such as the capacity and right to make decisions that affect their personal life; and social functioning, such as the ability to function and develop in different areas of life.

Until now this dimension of recovery has been little considered in studies that assessed the efficacy and effectiveness of different treatments, especially pharmacological. There is more data on the efficacy, effectiveness and efficiency of psychosocial interventions and the organisation of services on outcomes in quality of life, personal autonomy and social functioning. In order to achieve this recovery, in addition to acute treatment of symptoms and maintenance of treatment to avoid relapses, all those affected require to be empowered: introducing the family as a fundamental element and ensuring better organisation in the care of persons with schizophrenia. Empowerment has to take place simultaneously at the patient population and individual level, as it consists of a multidimensional social process through which individuals and groups achieve better knowledge and control over their lives; As a consequence, they can transform their social and political environment to improve their circumstances of daily life which are related to health.\textsuperscript{135}

The family dimension has begun to be considered in recent years, in the sense that the family and the patient form an indissoluble unit for treatment action with the aim of improving the progression and prognosis of the disease. It is necessary to detect homogenous groups of relatives and patients with schizophrenia to be able to intervene at family level with interventions based on the criteria of efficiency and effectiveness applied to the Spanish population and in our environment i.e. this would bear in mind our high-pressure healthcare situation; resource constraints, over-medicalisation, and lack of community resources. It is therefore necessary to provide healthcare and economic policies which are tailor-made for these circumstances.\textsuperscript{136}

Improving the organisation of care for people with schizophrenia implies\textsuperscript{138}: providing the required integrated, evidence-based care that will meet the needs of physical and mental healthcare; providing support for people with schizophrenia to live in their usual environment, and developing mechanisms to help them navigate complex employment and social benefits systems; providing specific support, information, and educational programmes for family members and caregivers in order that they can provide care for individuals with schizophrenia in a manner that minimises disruption to their lives; regularly reviewing and improving care procedures for people with schizophrenia, with all interested parties involved, including organisations that support people with schizophrenia; providing support which is equivalent to the impact of the disease, researching and seeking new treatments, and running adequately and regularly funded awareness campaigns that would form a permanent part of the action plans.

Regarding pharmacological treatment, in general terms, patients receiving this treatment have a better quality of
life than those who do not receive it. Second-generation antipsychotics would have advantages in this regard compared to first-generation antipsychotics, and long-term injectable antipsychotics appear to have advantages over oral antipsychotics in terms of better functioning, quality of life and patient satisfaction. However, some studies do not show any benefit for long-term injectable antipsychotics versus oral antipsychotics, in terms of reducing relapse.

A related aspect that is increasingly relevant is the concept of "recovery from the patient’s perspective". This concept goes beyond the improvement in quality of life or subjective experience, and implies the patient’s overall perception of feeling recovered as a person, in all senses. That is, it places the subject-patient and his own subjective perception at the centre. This aspect has been gaining importance in recent years, to become an essential aspect in the planning of mental healthcare services in many countries. In a recent qualitative study with Delphi groups on 381 patients diagnosed with schizophrenia, items were recorded which were related to the concept of recovery from the perspective of the patient. The first two most frequently cited items were: 1) to achieve an acceptable quality of life and 2) having a positive feeling towards oneself.

In summary, this dimension needs to be incorporated as a fundamental measure of outcome, as regards both the preparation of individual care plans, and the treatments made available to those affected and their care provider organisation. To that end, their monitoring in usual clinical practice, and the use of this in research are key elements which require a prior critical and consensus-based assessment of the different scales existing.

Inclusion

According to biopsychosocial models, stigma is revealed in three aspects of social behaviour: stereotypes, understood as general agreement as to what characterises a group of people; social prejudices, that is, the application or emotional experience of these stereotypes; and effective discrimination, that is, the behaviour of rejection towards those groups. The person with mental illness must face a threefold difficulty in recovering: the illness itself, the prejudices and discriminations he receives as a result of it (social stigma) and self-stigma (or internalised stigma), and the anticipated discrimination that the patient believes will occur before they have experienced it. The prevalence of internalised stigma is 41.7%, and 40–79% of the relatives of patients with severe mental disorders are considered stigmatised. The consequences of stigma are severe, ranging from inhibition when seeking help or treatment for their illness to a negative impact on the quality of life of the patient and their caregivers. The stigma assessment has so far focussed on internalised stigma, using scales such as the Internalised Stigma Scale (ISS) or the Internalised Stigma Inventory of Mental Illness (ISI). However, it is also necessary to assess stigma within the general population with questionnaires such as the Mental Health Knowledge Scale (MAKS), the Community Attitudes towards the Mentally Ill (CAMI) scale or the Informed Behaviour Scale and Intended (RIBS).

The fight against stigma should be a key element in mental healthcare plans in the coming years. This fight against stigma should include interventions on: 1) the patient: with strategies aimed at optimising pharmacological treatment, psychoeducational strategies to improve knowledge of the disease, managing stress, improving cognitive deficits, preventing relapses and consumption of substances, strategies to improve personal skills and promote autonomy, involving the patient in identifying discriminatory practices, and promoting access to and use of new technologies; 2) the family: with psychoeducational strategies aimed at improving knowledge and management of the disease, involving families in the treatment process; 3) health professionals: with training for social action as a model of tolerance and acceptance of people with mental disorders; 4) health authorities: promoting legislative and policy initiatives that favour the inclusion of mentally ill patients and developing management plans which would meet the expectations and needs of users; and 5) the media: through activities that promote the dissemination and implementation of existing guidelines for the treatment of mental health information and, among others, seeking to avoid transmitting a negative impression of mental illness.

Conclusions

What is required is a change in the paradigm of schizophrenia treatment, where the different dimensions reviewed in this article are considered, not only in terms of parameters of efficaciousness, but also of effectiveness and efficiency. There are numerous needs which are not covered in the healthcare received by persons with schizophrenia, but that they do require. The individual, family and social costs are very high. Studies are needed that would include key outcome variables which are ecological, pragmatic and relevant to the quality of life and functioning of persons with schizophrenia, their families and society.

The Rethinking working group, on an interdisciplinary basis, has contributed, through the collaboration of all parties involved (psychiatrists, clinical psychologists, nursing personnel, health economics specialists, health managers, representatives of scientific societies and patient associations, as well as family members and caregivers), a consideration and set of proposals to prioritise lines of action, including parameters of effectiveness and efficiency, that would address the unmet needs identified. Table summarises the main conclusions of each of the dimensions analysed.

The growing scientific advances in the field of schizophrenia, improvements in treatment and care, and the greater information available to those affected and their caregivers, are leading us to a new stage characterised by growing optimism about the future of those who suffer from this condition. Our responsibility as experts must be to lead the movement to respond to the needs identified, effectively and efficiently. It is the desire of the Rethinking movement to implement concrete action plans over the next
few years to continue to improve the lives of people with schizophrenia.

**Ethical responsibilities**

**Protection of people and animals.** The authors state that no experiments have been performed on humans or animals for this research.

**Confidentiality of data.** The authors state that no patient data appears in this article.

**Right to privacy and informed consent.** The authors state that no patient data appears in this article.

**Financing**

Otsuka and Lundbeck have provided financial support to hold working meetings but have not participated in any way in the manuscript or in its design, content or conclusions.

**Conflicts of interest**

Benedicto Crespo-Facorro has received consulting and lecture fees from Janssen Johnson & Johnson, Lundbeck, Roche and Otsuka Pharmaceuticals.

Miguel Bernardo has received consulting fees or research grants from ABBiotics, Adamed, Almirall, Amgen, Boehringer, Eli Lilly, Ferrer, Forum Pharmaceuticals, Gedeon, Hersill, Janssen-Cilag, Lundbeck, Otsuka, Pfizer, Roche and Servier. He has obtained research grants from the Carlos III Health Institute, the Spanish Ministry of Science and Innovation, the Ministry of Economy and Competitiveness, the Spanish Centre for Biomedical Research in the Mental Health Network (CIBERSAM), the Government of Catalonia, the Department of Universities and Research Department D’Economia i Coneixement (2014SGR441), and the 7th Framework Programme of the European Union.

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