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INTERVENTIONS TO IMPROVE THERAPEUTIC ADHERENCE IN SUBJECTS WITH SCHIZOPHRENIA

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Actualmente existe un amplio consenso en afirmar que la falta de adherencia terapéutica es uno de los principales problemas del tratamiento de la esquizofrenia. Las elevadas tasas de no adherencia a la medicación antipsicótica que presentan los sujetos con esquizofrenia ponen en entredicho la eficacia de la farmacoterapia y se relaciona con un peor pronóstico de la enfermedad. El presente trabajo tiene como objetivo ofrecer una visión general sobre las características y la eficacia de las intervenciones diseñadas para mejorar la adherencia a la medicación en la esquizofrenia. Así mismo, se revisan los datos disponibles acerca de los aspectos más relevantes de la adherencia con el objetivo de examinar y conceptualizar sus características y particularidades.

Palabras clave: Esquizofrenia, Adherencia, Tratamiento de adherencia, Factores, Consecuencias, Prevalencia.

Today it is broadly accepted that the lack of therapeutic adherence is one of the main problems in schizophrenia treatment. High non-adherence rates to antipsychotic medication call into question the efficacy of pharmacotherapy and are related to a worse prognosis of the disease. The purpose of the current report is to give a general overview of the characteristics and the effectiveness of interventions designed to improve medication adherence in schizophrenia. In addition, the available scientific literature on the main aspects of adherence is reviewed in order to examine and conceptualize its characteristics and attributes.

Key words: Schizophrenia, Adherence, Adherence treatment, Predictors, Consequences, Prevalence.

THE TERM ADHERENCE

The first and main problem that we find in the literature on therapeutic adherence lies in the difficulties posed by its own defining characteristics (Velligan et al., 2006). Initially, in order to establish an adequate definition of adherence, it is necessary to differentiate it from the concept of compliance. Although the two concepts are used interchangeably, they present important differences. Adherence refers to a collaborative relationship between patient and practitioner in the achievement of therapeutic objectives, while compliance implies the adoption of a passive and obedient role of the patient towards the clinician (Compton, 2006).

Thus, adherence is a complex phenomenon, with a broad diversity of profiles, which is why we currently find a wide variety of defining criteria in the literature (see Table 1). Given this problem, the American Psychological Association (APA) has recently published an international consensus document that establishes the following criteria: patients who take more than 80% of the medication are classified as adherents, those who take between 80 and

20% are categorized as partial adherents and those who take less than 20% are deemed non-adherents.

The defining complications of the concept of adherence reinforce the difficulties of the evaluation process. Today, different methods are used to examine adherence to treatment, but each of them presents a series of limitations (Velligan et al., 2006). Thus, despite the fact that interviews and psychometric scales are the most used

TABLE 1
COMPARISON OF DEFINITIONS OF ADHERENCE

Author and year	Sample	Definition of adherence
Eaddy et al., 2005	N = 7,864	✓ Partially adherent (compliance <80% medication) ✓ Adherent (compliance 80-100% medication) ✓ Excessively adherent (compliance > 125% medication)
Morken et al., 2008	N = 50	✓ Good adherence classified as less than a month without taking medication.
Ahn et al., 2008	N = 36,195	✓ Adherent and partially adherent (compliance > 80% medication) ✓ Non-adherent (compliance <80% medication)
Kozma et al., 2009	N = 1,499	✓ Medication possession ratio
Laan et al., 2010	N = 477	✓ Medication possession ratio

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tools (Singh, Massey, Thompson, Rappa, & Honeywell, 2006), it is argued that there is no single technique that is capable of correctly assessing adherence, and many authors recommend the use of at least two different methods (one objective and one subjective) in each evaluation process (Acosta, Hernández, Pereira, Herrera, & Rodríguez, 2012).

PREVALENCE AND CONSEQUENCES OF THE LACK OF ADHERENCE

The data on the prevalence of lack of adherence among subjects with schizophrenia vary markedly in the different studies (see Table 2). This fact corresponds mainly to the absence of clearly established defining criteria and the difficulties in its evaluation. However, it is estimated that the rates of lack of adherence range between 20% and 89%, so there is no doubt that the prevalence of this phenomenon is very high among subjects with schizophrenia (Coldham, Addington, & Addington, 2002). Moreover, many studies have shown how adherence problems are associated with a series of negative consequences for the patients themselves as well as for health systems and society. The main ones are:

1) Relapse. Most studies show that lack of adherence is one of the factors most associated with relapse (Novick et al., 2010) and hospitalizations (Morken, Grawe, & Widen, 2007; Ahn et al., 2008). Specifically, it is estimated that non-adherent patients have a risk of

relapsing that is 3.7 times greater than subjects with good adherence to the treatment (Zygmunt, Olfson, Boyer, & Mechanic, 2002).

- 2) Forecast.** The lack of adherence shows a strong relationship with the increase of psychotic symptoms, longer periods of remission (Higashi et al., 2013), increased suicide rates (Novick et al., 2010; Higashi et al., 2013), increased cognitive deterioration, and poorer quality of life (Ascher-Svanum et al., 2006).
- 3) Costs.** The lack of therapeutic adherence translates into a notable increase in the use of health services. In fact, it is estimated that 40% of the cost associated with the treatment of schizophrenia is attributed to the lack of adherence, involving an annual expenditure of 400 million pounds in the United Kingdom and more than ten billion dollars in the United States (Perkins, 2002).

FACTORS THAT INFLUENCE ADHERENCE

The lack of adherence to medication includes a complex range of patient attitudes and behaviors, which range from refusal of treatment to partial or irregular compliance with daily medication doses (Higashi et al., 2013). The main factors that have been associated with lack of adherence are:

- 1) Insight.** This is the psychopathological symptom that has the closest relationship with adherence to medication. Patients with low awareness of illness have very low adherence rates (Hui et al., 2015).
- 2) Effects of the medication.** The adverse effects of the drugs are well documented and are shown as one of the most important factors that motivate the lack of adherence. Furthermore, there are no differences between typical antipsychotics and atypical antipsychotics, with a notable exception for clozapine (Hofer & Fleischhacker, 2014).
- 3) Therapeutic alliance.** A good therapeutic alliance is one of the factors most associated with adherence to treatment (Novick et al., 2010; Acosta et al., 2012). However, this agreement could be bidirectional.
- 4) Substance abuse.** Although some studies have not found positive correlations (Robinson et al., 2002), most authors agree that the consumption of alcohol and other drugs increases the lack of adherence to treatment (Hudson et al., 2004; Novick et al., 2010).
- 5) Lack of support.** The patient's social support system seems to play a vital role in the process of adherence to medication (Singh et al., 2006; Hui et al., 2015).

TABLE 2
RATES OF PREVALENCE OF ADHERENCE

Author and year	Prevalence rate
Coldham et al., 2002	✓ 40.9% adherent subjects ✓ 19.9% partially adherent subjects ✓ 39.3% non-adherent subjects
Robinson et al., 2002	✓ 26% of subjects non-adherent during the first year of treatment ✓ 30% of subjects non-adherent after the first relapse
Hui et al., 2005	✓ 25% of subjects decide to stop taking the medication. ✓ 38% of subjects forget to take the medication.
Novick et al., 2010	✓ 28.8% of subjects non-adherent during three years of follow-up.
Hui et al., 2015	✓ 16.2% lack of adherence during the first year and 15.4% during the second.
Hui et al., 2016	✓ 17.6% of subjects non-adherent.



Subjects with relatives involved in the treatment (Coldham et al., 2002) and who have a high level of social activity (Novick et al., 2010) are more adherent.

- 6) **Severity of symptoms.** The severity of the positive symptomatology is another important element that contributes to the lack of adherence to treatment (Hudson et al., 2004; Hui et al., 2015). In contrast, subjects with anxious and depressive symptoms appear to be more adherent (Singh et al., 2006).
- 7) **Stigma.** The stigma of the disease is, according to the majority of subjects with schizophrenia, one of the main obstacles to adherence to treatment. (Hudson et al., 2004; Singh et al., 2006).
- 8) **Cognitive impairment.** Cognitive dysfunction in schizophrenia is well documented and has been significantly related to lack of adherence (Acosta et al., 2012; Singh et al., 2006). Specifically, deficits in verbal memory, executive functions, and attention seem to be the most relevant factors (Jeste et al., 2003).
- 9) **Onset of the disease.** Early onset of the pathology, and poor functioning during the premorbid phase and the active phase of the disorder are positively associated with lack of adherence (Coldham et al., 2002).

INTERVENTIONS TO IMPROVE THERAPEUTIC ADHERENCE

In recent decades, several interventions have emerged that aim to ensure that subjects with schizophrenia adhere correctly to pharmacological treatment (see Table 3). Next, we review the characteristics of the main interventions that currently exist, as well as the studies that have been carried out to analyze their efficacy.

Motivational interviewing

Motivational interviewing (MI) is a psychotherapeutic approach that seeks to help people recognize and deal with their potential and present problems (Miller & Rollnick, 2002). Its authors emphasize that MI does not deal with a set of techniques but rather it defines “the way of being” with the patient through a series of essential principles: (1) establishment of a collaborative relationship between patient and practitioner, (2) evocation of the internal motivations of the subject, and (3) respect for their autonomy. Thus, the use of MI as an intervention to improve adherence in subjects with schizophrenia relies on its effectiveness in incentivizing, motivating and maintaining the change in people’s behavior.

However, in the literature we do not find many studies that have evaluated the ability of MI as a single intervention to increase adherence to medication, and most research has focused on examining MI-based treatments that incorporate other cognitive-behavioral techniques. Five clinical trials have tested its effectiveness. Two of them did not present positive results in favor of MI-based treatments (O’Donnell et al., 2003; Byerly, Fisher, Carmody, & Rush, 2005), while two other studies showed that the intervention motivated a non-significant improvement in the awareness of illness and adherence to treatment of subjects (Hayward, Chan, Kemp, Youle, & David, 1995; Barkhof, Meijer, Sonnevile, Linszen, & de Haan, 2013). Finally, a single trial showed that the intervention was significantly efficacious in improving therapeutic adherence (Kemp, Kirov, Everitt, Hayward, & David, 1998).

Treatment adherence therapy

Treatment Adherence Therapy (TAT) is an individual intervention with a cognitive-behavioral approach. It is based on an empirical model that groups the determinants of lack of adherence into three categories: (1) lack of insight and rejection of treatment, (2) dissatisfaction with medication, and (3) lack of cognitive skills necessary to carry out the pharmacological treatment correctly, and it incorporates an intervention module for each of them: (a) motivational interview, (b) medication adaptation and (c) behavioral training techniques (Staring et al., 2010).

Nine studies have evaluated the effectiveness of this intervention. Two of them did not present significant results in favor of TAT, either in the reduction of symptomatology or in the increase of therapeutic adherence (Gray et al., 2006; Anderson et al., 2010). Also, another randomized controlled trial showed that the intervention was slightly more effective than the usual treatment in reducing psychotic symptoms and improving attitudes towards medication (Maneesakorn, Robson, Gournay, & Gray, 2007). The other six studies presented significant results on the efficacy of TAT. Two clinical trials showed that the intervention produced a significant reduction in the symptoms of the subjects but did not improve adherence to medication (Shulz et al., 2013), while a study conducted in 2013 showed that the intervention motivated a significant reduction in relapse rates, but did not provide data on adherence to



TABLE 3
CHARACTERISTICS AND RESULTS OF THE INCLUDED STUDIES

Type of intervention	Study	Design	Duration of intervention	Limitations	Results
MI	Hayward et al., 1995	Randomized and controlled N = 10. Experimental group (medication self-management therapy) N = 11. Control group (non-directive conversations)	2-3 sessions	✓ Small and inhomogeneous sample ✓ Absence of objective methods in the evaluation ✓ Short and unregulated treatment	Insignificant improvement of insight and adherence
MI	Kemp et al., 1998	Randomized and controlled N = 25. Experimental group (treatment compliance) N = 22. Control group (nonspecific therapy)	4-6 sessions of 20-60 minutes	✓ Absence of objective methods in the evaluation. ✓ Inhomogeneous sample. ✓ Little specification of the experimental treatment	Significant increase in adherence
MI	O'Donnell et al., 2003	Randomized and controlled N = 28. Experimental group (compliance treatment) N = 28. Control group (non-specific therapy)	5 sessions of 30-60 minutes	✓ Absence of objective methods in the evaluation ✓ 36% of the subjects refused to participate in the study	Non-significant differences
MI	Byerly et al., 2005	Randomized and uncontrolled N = 39. Experimental group (treatment compliance)	4-6 sessions of 30-60 minutes	✓ Small sample ✓ Absence of a control group	Non-significant differences
MI	Barkhof et al., 2013	Randomized and controlled N = 55. Experimental group (motivational interview) N = 59. Control group (health education)	8 sessions of 20-45 minutes	✓ Absence of objective methods in the evaluation ✓ 39% of the subjects refused to participate in the study	Non-significant increase in adherence
TAT	Gray et al., 2006	Randomized and controlled N = 204. Experimental group (TAT) N = 205. Control group (health education)	8 sessions of 30-50 minutes	✓ Poorly representative sample, incorporating already adherent subjects ✓ Absence of objective methods in the evaluation	Non-significant differences
AT	Maneesakorn et al., 2007	Randomized and controlled N = 16. Experimental group (TAT) N = 16. Control group (usual treatment)	8 sessions of 15-60 minutes	✓ Small sample and with good initial evolution ✓ Use of a single therapist	Significant improvement of psychotic symptomatology and attitude toward medication
TAT	Staring et al., 2010	Randomized and controlled N = 55. Experimental group (TAT) N = 47. Control group (usual treatment)	8 sessions of 15-60 minutes	✓ Small sample ✓ The experimental group received twice as many intervention sessions as the control group ✓ Absence of objective methods in the evaluation	Significant increase in adherence
TAT	Anderson et al., 2010	Randomized and controlled N = 12. Experimental group (TAT) N = 14. Control group (usual treatment)	8 sessions of 20-60 minutes	✓ Small sample ✓ Short follow-up period: 8 weeks ✓ Absence of objective methods in the evaluation	Non-significant reduction of psychotic symptoms. No differences in adherence
TAT	Brown et al., 2013	Randomized and controlled N = 35. Experimental group (TAT)	8 sessions of 20-60 minutes	✓ Small sample ✓ No direct assessment of adherence ✓ Absence of a control group	Significant reduction in relapse rates
TAT	Schulz et al., 2013	Randomized and controlled N = 72. Experimental group (TAT) N = 51. Control group (usual treatment)	8 sessions of 20-60 minutes	✓ Sample formed by the most adherent subjects ✓ Lack of regulation of intervention of control group	Significant reduction of symptoms but not adherence
TAT	Bormann et al., 2014	Randomized and controlled N = 38. Experimental group (TAT) N = 32. Control group (usual treatment)	8 sessions of 20-60 minutes	✓ Absence of objective methods in the evaluation ✓ Lack of regulation of the intervention of the control group ✓ Sample formed by the most adherent subjects	Significant reduction of symptoms but not adherence



TABLE 3
CHARACTERISTICS AND RESULTS OF THE INCLUDED STUDIES (CONTINUED)

Type of intervention	Study	Design	Duration of intervention	Limitations	Results
TAT	Chien et al., 2015	Randomized and controlled N = 57. Experimental group (TAT) N = 57. Control group (usual treatment)	8 sessions of 20-60 minutes	✓ Absence of objective methods in the evaluation ✓ Socio-demographic characteristics of the sample	Significant improvement in adherence and symptomatology
TAT	Dikec et al., 2016	Randomized and controlled N = 15. Experimental group (TAT) N = 15. Control group (usual treatment)	8 sessions of 20-60 minutes	✓ Absence of objective methods in the evaluation ✓ Use of a single therapist	Significant improvement in adherence
ACE	Uzenoff et al., 2008	Randomized and controlled (Pilot) N = 12. Experimental group (ACE) N = 12. Control group (usual treatment)	14 sessions	✓ Absence of objective methods in the evaluation ✓ Small sample	Significant improvement in attitudes toward drugs and symptomatology
Community intervention	Gray et al., 2004	Randomized and controlled N = 29. Experimental group (subjects with nurses who had taught the training program) N = 24. Control group (subjects with nurses who had not taught the training program)	Unknown	✓ Lack of control over the effect of training time ✓ One third of the subjects did not complete the study	Significant increase in adherence
Community intervention	Hudson et al., 2008	Randomized and controlled 3 medical centers. Experimental group (received a specific guide of strategies for the treatment). 3 medical centers. Experimental group (received a basic guide of strategies for the treatment)	4 sessions in 6 months	✓ Absence of objective methods in the evaluation	Significant increase in adherence
Community intervention	Beebe et al., 2008	Randomized and controlled N = 15. Experimental group (TIPS) N = 4. Control group (usual treatment)	3 months	✓ Small and decompensated sample ✓ Use of a single evaluation method	Significant increase in adherence
Community intervention	Beebe et al., 2016	Randomized and controlled N = 10. Experimental group (daily text messages) N = 10. Experimental group (TIPS) N = 10. Experimental group (daily text messages and TIPS)	Unknown	✓ Small sample ✓ Use of a single evaluation method ✓ Inclusion of subjects treated with "depot" medications	Non-significant differences
Mixed intervention	Petersen et al., 2005	Randomized and controlled N = 205. Experimental group (mixed intervention: assertive treatment, family participation, and social skills training) N = 164. Control group (usual treatment)	Two weekly sessions for 18 months and skills training of unknown duration	✓ The evaluators knew which group each subject belonged to ✓ Possible wear due to the breadth and duration of the study	Significant increase in adherence Non-significant differences Significant increase in adherence
Mixed intervention	Morken et al., 2007	Randomized and controlled N = 25. Experimental group (mixed intervention) N = 25. Control group (usual treatment)	8 weekly sessions, 22 monthly sessions and individual sessions of unknown duration	✓ Scarce documentation on the interventions carried out ✓ Use of a single evaluation method	
Mixed intervention	Dahan et al., 2016	Randomized and controlled N = 31. Experimental group (mixed intervention: medication adaptation, CBT, MI and psychoeducation) N = 32. Control group (usual treatment)	6 sessions of 20-40 minutes		



medication (Brown, Gray, Jones, & Whitfield, 2013). Lastly, three randomized controlled trials showed significant results in the increase of therapeutic adherence in favor of TAT (Staring et al., 2010; Chien, Mui, Cheung, & Gray, 2015; Dikec & Kutlu, 2016).

Adherence therapy, coping and education

Adherence-Coping-Education (ACE) therapy is an intervention designed to increase disease awareness and improve adherence in people with schizophrenia. The therapy is based on the health belief model and its application has four main phases: (a) establishment of therapeutic alliance, (b) promotion of adherence to treatment, (c) development of a therapeutic maintenance plan, and (d) rehabilitation. In the literature we found one single pilot test that has tested its effects. The results obtained showed that the intervention produced a significant improvement in the symptomatology and attitudes toward the drugs (Uzenoff, Perkins, Hamer, Wiesen & Penn, 2008).

Community interventions

Community interventions for subjects with schizophrenia have a double task: to bring the patient closer to the community and to approach the subject's social group to promote processes of acceptance of the psychopathology. Their effects on the improvement of medication adherence have been evaluated in two different studies. In the first, a training program was examined in which the adherence to treatment model was taught, and it was evidenced that the subjects that had nurses who had taught the program had significantly higher adherence rates (Gray, Wykes, Edmonds, Leese, & Gournay, 2004). In a similar study, three medical centers received a basic guide to strategies for the treatment of schizophrenia, while three others were given a specific and improved guide. In this case, the results revealed that patients at medical centers with improved interventions had almost twice the medication adherence (Hudson, Owen, & Thrush, 2008).

A similar treatment is Telephone Intervention Problem Solving (TIPS), a therapeutic tool that provides support to subjects with schizophrenia, aims to promote the resolution of problems, offer coping strategies and provide reminders. Two randomized controlled trials have examined its efficacy in improving adherence to treatment. The first one compared the effects of the telephone intervention with the usual treatment and did

not obtain significant results (Beebe, Smith, & Crye, 2008). The second one compared the effects of the telephone intervention and the sending of messages, and did not present significant differences either (Beebe, Smith, & Phillips, 2016).

Mixed interventions

The diversity of treatments that have shown therapeutic capacity to improve adherence to medication in subjects with schizophrenia has motivated the emergence of mixed interventions that integrate and combine different strategies. Three studies have evaluated their effectiveness. One of them compared the effects of the mixed intervention with the usual treatment and showed that, after one year of follow-up, the patients who had received the mixed intervention had significantly higher medication adherence rates (Petersen, Jeppesen, Thorup, Abel, & Øhlenschlaeger, 2005). However, two years later, a similar study was not able to replicate the results (Morken et al., 2007). Recently, a new clinical trial showed that a mixed intervention applied to 60 patients with schizophrenia was significantly more effective than the usual treatment in increasing therapeutic adherence (Dahan, Behrbalk, & Greenberger, 2016).

Pharmacological interventions

The way of prescribing the medication, taking into account the characteristics of the pharmacotherapy, is an essential aspect in promoting optimal adherence. In this sense, the main pharmacological interventions include: (1) optimization of dosage to minimize symptoms, (2) application of an adequate trial period before increasing doses or adding other drugs, (3) use of injections of long duration, (4) reduction of doses or modification of medication to minimize side effects, (5) simplification of treatment, and (6) evaluation of the ingestion of tablets (Compton, 2006). The pharmacological intervention to be chosen to improve adherence may vary in each case (Singh et al., 2006).

DISCUSSION

This review has focused on examining the interventions that are currently used to improve medication adherence in subjects with schizophrenia. First, it should be noted that the lack of adherence is one of the biggest problems of the illness. The prevalence rates of this phenomenon are very high among subjects with schizophrenia and the



consequences that it causes are devastating for their prognosis. Moreover, when examining adherence to treatment we find that the great diversity of definitions and the lack of consensus in the evaluation process are clearly problematic aspects that require further study.

With regard to interventions, it is noted that there is no single treatment that facilitates the improvement of adherence to medication, however there are different interventions that show therapeutic benefits. In this sense, three elements seem to play a fundamental role: (1) the establishment of a collaborative therapeutic relationship between patient and clinician, (2) the individualized study of the factors that motivate adherence problems in each case and dealing with these, and (3) interdisciplinarity in the treatment.

The establishment of a collaborative therapeutic relationship between patient and clinician is already reflected in the definition of adherence itself and has its maximum exponent in the motivational interview. Although the studies of this intervention present results that provide little clarification, MI provides a promising and essential approach for dealing with adherence. Furthermore, MI is one of the basic elements of TAT, and ACE, interventions that show better efficacy rates.

On the other hand, determining the impact caused by each of the factors associated with lack of adherence is essential in designing interventions. TAT postulates this line of approach but only offers strategies for three different factors and requires further investigation. Moreover, community interventions seem to be useful for subjects who have a deficit of skills and/or lack of support to carry out the pharmacological treatment correctly, and mixed interventions reaffirm the idea of multifactoriality, incorporating and integrating different treatments. Furthermore, the fact that pharmacological interventions are as necessary and insufficient as psychosocial interventions shows that adherence to medication must be a therapeutic objective for all clinicians.

Therefore, it is concluded that interventions to improve adherence are essential to ensure a good treatment of schizophrenia. Moreover, an approach is required in which the treatment of adherence is not limited to isolated interventions, but is part of the general attitude of all clinicians who deal with this type of disease. Thus, all the therapeutic agents involved in the case should follow the same attitudinal orientation towards the patient based on listening, mutual respect and collaboration, as well as the

other basic postulates of the motivational interview. This would include the design of more individualized therapeutic approaches, always based on the establishment of a therapeutic bond based on a relationship in which the patient's vision with respect to what is happening to them is considered and evaluated, as well as their opinion regarding the proposed treatments. This evaluation would not only lead us to detect the motivation to change and awareness of the problem, but also their expectations, objectives, desires, priorities and reticence. It is on this basis that the clinician should consider the therapeutic plan.

Based on this, the therapeutic work would be to go forward together towards the development of a meeting between the vision of the subject and that of the clinician. It is essential to listen and understand the reasons that lead the subject to be reluctant to treatment, validating them while offering information or alternatives to each of them. To assess together the pros and cons, and give the opportunity to try different options and change when appropriate. The genuine listening and understanding of the patient's vision of their reality has a therapeutic effect in itself, so we often see that this alone is enough for some subjects to pay attention to the therapeutic recommendations to which they were initially reluctant. Being flexible in the dosage, route of administration and simplification of the intakes will also contribute to a better adherence. Finally, when instrumental reasons are detected in non-adherence, it will be essential to provide adequate means to alleviate them.

To sum up, it is important not only to continue to advance in the study of the facilitating factors of therapeutic adherence in subjects with schizophrenia, but also to ensure the dissemination and application in clinical practice of some of the fundamental aspects that we already know about it.

CONFLICT OF INTEREST

There is no conflict of interest.

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