REVISTAPORTUGUESADE PSIQUIATRIA ESAÚDEMENTAL
Volume 3, 2018, 24-33

REVIEW ARTICLE

Treatment adherence in schizophrenia: a literature review

NELSON DESCALÇO*
University of Lisbon Faculty of Medicine

PEDRO AFONSO
Department of Psychiatry and Psychology, Faculty of Medicine, University of Lisbon

Abstract: Introduction: Evaluating adherence to treatment with antipsychotic agents in patients with schizophrenia is a challenge for any psychiatric doctor, given its inherent subjectivity. Despite this, nonadherence to treatment is prejudicial to the clinical course of the disease, resulting in a greater risk of acute exacerbations of illness and hospital admissions. The aim of this study is to review the current literature on factors that influence adherence to antipsychotic treatment in patients with schizophrenia.
Methods: The literature, written in English between 2006 and 2016 and available in full in PubMed/MEDLINE, evaluating potential risk factors for treatment compliance in adult patients (over 18 years of age) with schizophrenia, was reviewed by searching on the keywords: *adherence*, *nonadherence*, *compliance*, *noncompliance*, *schizophrenia*, *psychosis*, *antipsychotic*, *neuroleptic*.
Results: Thirty-nine studies were included in the final review. The average level of treatment adherence was 32%. The following risk factors for nonadherence to treatment were identified: young age, substance abuse, psychotic psychopathology present, absence of insight into the disorder and the need for treatment, negative attitudes to treatment, poor doctor-patient relationship and lack of social and family support.
Conclusions: Interventions aimed at improving treatment adherence must be individualised for each patient, on the basis of a full clinical history, so that all the individual aspects contributing to this variable can be appropriately assessed.

Keywords: adherence, nonadherence, compliance, noncompliance, schizophrenia, psychosis, antipsychotic, neuroleptic

1. Introduction

1.1. Adherence – definition and measurements

Treatment adherence is normally defined as the degree of agreement between a patient's behaviour and the guidance of the physician or another health professional in relation to a certain treatment; it is easily understood as a dichotomous variable (is the patient adhering to the treatment?) [1-3]. This is a definition that focuses strictly on compliance. It does not make a distinction between behaviour (did the patient actually take the medication?) and attitude to therapy (did the patient want to stick to the treatment?) [1].

In truth, treatment adherence should be understood as a set of dynamic behaviours that vary over time in the same patient [4, 5]. According to the health belief model, the probability of a patient complying with a given treatment or not is the product of a subjective comparison of the risks and benefits of treatment according to the patient's expectations and goals for it [6]. This subjective assessment by patients depends on factors like their perception of their health, the benefits of treatment, the obstacles to compliance that they face (adverse effects, the need to keep to a certain timetable, even cost) and other external factors [7]. When analysing all the factors that patients assess in their context, the probability of compliance with treatment is higher if the benefits outweigh the negative aspects.

Evaluating treatment adherence is a challenge present in the daily work of any doctor. Direct or indirect methods can be used. Direct methods (counting tablets, measuring the concentration of the drug/metabolites in blood or urine, or electronic systems like the Medication Event Monitoring System – MEMS®) are considered the most reliable, despite the fact that their use is limited by individual pharmacokinetic and pharmacodynamic variations, their higher cost and their more intrusive nature [1].

On the other hand, indirect (or subjective) measures of compliance are more widely used in clinical practice, as they are relatively easy to apply (asking patients about

* Correspondence to: ndescalco@gmail.com

their adherence, assessing clinical response or even consulting written records that patients have been instructed to keep). However, their validity is more questionable, and so the risk of overestimating compliance is real and should not be overlooked [8].

Noncompliance with treatment is a common behaviour in clinical practice; it is a source of concern of growing importance worldwide. In developed countries, treatment adherence rates in the region of 50% are observed in chronic diseases like asthma and diabetes [9]. In acute conditions compliance rates are typically higher, as the need for treatment is transient and time-limited [1].

In patients with a psychiatric pathology, levels of adherence to treatment are typically lower than in patients with organic pathologies [10]. In patients with depression, approximately half autonomously discontinue treatment three months after it starts, without consulting a physician; in patients with bipolar disease, the level of compliance may be around just 35%, principally in those with active psychosis [1, 10].

1.2. Treatment adherence in patients with schizophrenia

Schizophrenia is a chronic illness with a considerable social impact that affects more than 23 million people worldwide [11]. Although its clinical course is highly variable, it typically manifests in young individuals at the end of adolescence/start of adult life and is distributed evenly across the two genders, although the first manifestations of the disease occur earlier in the males than females.

In patients with schizophrenia, antipsychotics are one of the essential foundations of treatment of this pathology [12] and many factors have been studied for a possible association with low levels of treatment adherence. Psychotic symptoms and cognitive deficits affect patients' perception, as well as their ability to plan and act, and so are a decisive factor in treatment compliance in patients with schizophrenia [6]. According to the literature, levels of low adherence are similar to those seen in other chronic diseases, with half of patients being included in the low treatment compliance group [7]. Given the chronicity of treatment, some studies report low adherence rates of between 75% and 90% within 1 to 2 years of most recent hospital admission for psychiatric illness [13].

First-generation antipsychotics (like haloperidol and chlorpromazine) are very effective drugs in controlling psychotic symptoms. However, they are associated with the occurrence of adverse effects, particularly extrapyramidal symptoms, that are a source of concern because of the high risk of discontinuation of treatment. Second-generation antipsychotics (such as, for example, clozapine, risperidone and quetiapine) are associated with a lower incidence of extrapyramidal effects, although other secondary effects are observed (such as weight gain, diabetes and dyslipidemia) that also have a negative influence on treatment adherence [14, 15]. Delayed-release antipsychotics (administered via the intramuscular route every 2 to 6 weeks) have since been developed. In addition to keeping serum levels of antipsychotics more stable over time (as they are less dependent on treatment adherence), they also make it easier to identify patients who discontinue treatment [16].

The consequences of nonadherence to treatment in schizophrenia are multiple and seen at various levels. They have implications for stabilisation of the disorder, in particular because of the increased risk of psychotic episodes and hospital readmissions, which in turn worsen prognosis [17, 18]. For the patient, nonadherence can result in absence of response or partial response to treatment, with a consequent increase in the frequency of recurrence or aggravation of symptoms and the need for hospital admission to control psychopathology [3]. The relationship between nonadherence and increased risk of hospitalisation is mentioned consistently in the literature [17]; nonadherence shortly after most recent admission is a strong predictor of early readmission to hospital [18].

Remission of symptoms proves a more demanding clinical challenge with every relapse: cumulatively worse functional outcomes and cognitive deficits are seen over the course of the clinical evolution of patients who repeatedly fail to comply with treatment [17, 19]. In this way, the costs associated with treatment of schizophrenia increase significantly in comparison with patients who follow the treatment plan, both because of the higher number of admissions and because a longer period of admission is required to stabilise the clinical picture. In addition, noncompliance is associated with lower quality of life and higher levels of patient dissatisfaction, as well as more risky behaviours (because of consumption of alcohol and narcotics) that can have a negative impact for the individual and on society [20]. It is clear that the prognosis in schizophrenia is jeopardised by noncompliance with the treatment plan, since in addition to increasing the risk of acute exacerbation of the disease, it can also lead to the chronic presence of psychotic symptoms [21]. Lastly, the risk of suicide increases by a factor of four in patients who do not adhere to treatment; death by suicide is a significant cause of premature death in patients with schizophrenia [3].

2. Aims

The aim of this paper is to review the current literature on factors that influence treatment adherence in patients with schizophrenia who are medicated with antipsychotics.

3. Materials and Methods

A systematic review of the literature in English was conducted by searching in PubMed/MEDLINE between 2006 and 2016 using the following keywords: *adherence*, *nonadherence*, *compliance*, *noncompliance*, *schizophrenia*,

psychosis, *antipsychotic*, *neuroleptic*. The review included all articles with full text available in English that were original papers, with the purpose of assessing the impact of different risk factors on treatment adherence in schizophrenia in adults (over 18 years of age). Other exclusion criteria: studies with a sample smaller than 100 elements; if a clinical case, only the abstract available; editorials; unpublished papers; literature reviews.

The articles selected were evaluated according to their importance and their contribution to the main purpose of the review, resulting in a sample of 39 articles. The information gathered was then organised into categories of factors that influence treatment adherence: (a) patient-related factors, (b) treatment-related factors and (c) environment-related factors.

4. Results

4.1. Factors that influence treatment adherence

4.1.1. Patient-related factors

In the majority of cases, patients' sociodemographic characteristics (namely ethnicity, gender and marital status) do not appear to influence their level of adherence to treatment, given that no association is consistently reported among the studies analysed. However, younger patients appear to be at greater risk of not complying with therapy [22-28]. On the other hand, abuse of substances like alcohol and narcotics is related to nonadherence to treatment [25, 27, 29-34]. The presence of addictive behaviours (at the onset of the disorder or in the course of its clinical progress) appears to have a positive predictive value for nonadherence and consequently they correlate with a worse prognosis [25, 27, 30, 33-35]. The prevalence of dependencies in patients with schizophrenia is particularly high, which makes this factor highly significant in the evaluation of treatment adherence.

The influence of psychopathology is recognised and well documented in the literature [22, 23, 38-44, 24, 26, 29, 31-33, 36, 37]. The presence and severity of psychotic symptoms reliably predict nonadherence [22, 23, 45, 24, 29, 32, 33, 38, 39, 41, 44]. Persistence of psychotic symptoms may also be indicative of failure of the therapeutic regimen used, and should for this reason be carefully analysed. Some studies also suggest that the content of psychotic thoughts may influence treatment adherence, particularly if the patient exhibits delusions of grandeur, persecutory delusions or even delusions of poisoning [2]. In addition, some studies indicate that patients who comply with treatment show fewer depressive symptoms; the evidence is still thin however and further investigation is required [23, 24, 40].

Patient insight, i.e. the ability of patients to acknowledge their mental illness and their need for treatment or not, can prove to be one of the biggest obstacles to therapeutic success. Lack of insight is predictive of poor treatment adherence; on this the investigations undertaken agree [22, 24, 47-50, 26, 30, 32, 37, 40, 43, 44, 46]. A patient's attitude to treatment also has a major impact on therapeutic compliance, and the literature is unanimous in stating that negative attitudes, at any stage of the clinical course of the disease, correlate with low adherence [22, 26, 30, 37, 41, 44, 46, 48, 51]. Lack of insight and negative attitudes to treatment are an important focus of psychoeducational strategies that seek to promote better adherence [3].

The majority of studies do not appear to correlate patients' cognitive level with their level of treatment adherence [37, 45, 47, 49, 51]. However, limitations on executive functions and verbal memory may be correlated with poor compliance with the treatment plan [40, 52]. It is possible that verbal memory does not independently influence adherence, but that it has an effect by contributing to the clear correlation between lack of insight and nonadherence [43].

The patient's level of functioning appears to be directly related to treatment adherence; however the patient's subjective perception of quality of life does not appear to influence this measurement [9, 24, 30, 51].

The impact of patient follow-up (outpatient *versus* inpatient) and of compulsory admission to a psychiatric unit requires further investigation [36, 53-55]. Moreover, severity of illness appears to influence treatment adherence, but age at onset of disease shows no relationship with compliance [37, 49, 51, 56, 57]. Data as regards "duration of untreated psychosis" are contradictory and do not permit any conclusions to be drawn [30, 51]. The existence of a history of aggressive behaviour and or abuse and/or childhood maltreatment appears also to correlate with lower levels of treatment adherence, but few studies have sought to investigate the impact of these variables [31, 39, 42]. As only one study has investigated the impact of religious practice on treatment it is not possible to draw conclusions in this area [29].

4.1.2. Factors related to pharmacological treatment

The class and administration regimen of antipsychotics do not appear to influence adherence to the treatment plan [23, 28, 34, 44, 49, 51]. However, where a statistically significant association is detected, it tends to favour use of atypical antipsychotics over first-generation antipsychotics and use of combination therapy [22, 27, 31]. Within the same class (particularly among the second-generation antipsychotics), no significant differences in treatment compliance have been observed with different antipsychotics [22, 24, 27].

The literature included in this review does not allow conclusions to be drawn in relation to the impact of prolonged-release agents on treatment adherence, as few studies have focused on this comparison: more attention has been paid to differences between typical and atypical agents [23, 27].

When assessed globally, the relationship between the secondary effects of antipsychotics and treatment adherence appears to be controversial, and correlations, where observed, are not consistent [31, 41, 44, 49, 54, 58]. Some studies suggest that patients who comply with treatment to a greater degree report adverse effects more frequently [24, 37, 45], while others observe the opposite relationship [22, 48, 59].
Patient satisfaction with treatment was addressed as an independent variable in some studies, highlighting that greater satisfaction with and acceptance of treatment are correlated with higher levels of treatment adherence [23, 56].

4.1.3. Environment-related factors

The therapeutic relationship between physician and patient appears to be a fundamental and generally acknowledged element in optimising the patient's treatment adherence; there is some evidence that the quality of this relationship is predictive of the patient's level of compliance [37, 39, 44, 50, 57, 60]. It is suggested in the literature that both the physician's perception and that of the patient as to the quality of the relationship established independently affect treatment adherence [60]. In some cases, studies assessed the impact of components of the doctor-patient relationship (such as trust in the physician or clear communication with shared understanding, i.e. the ability to ensure that the proffered information is understood by the patient) that were responsible for direct and indirect effects (by modifying attitudes to treatment) on treatment adherence [57, 60].
Family and social support correlates with higher levels of adherence to treatment; the family's attitudes to treatment (if positive) can also be beneficial to treatment compliance [37]. There is evidence that patients with better treatment adherence perceive a greater involvement of family in their recovery [36].
Other environmental factors, such as racism or stigma associated with mental illness, may be items of relevance to treatment adherence, but were evaluated in only a small number of studies [61, 62].

5. Discussion

The most powerful patient-related predictors of nonadherence to treatment studied in this review were the following: young age, concomitant substance abuse, active presence of psychotic symptomatology, absence of insight and presence of negative attitudes to treatment.
Some of these correlated factors, such as absence of insight and attitude to treatment are fairly intuitive, as it is easy to understand from the health beliefs model that patients unable to recognise that they have an illness are unlikely to acknowledge that they need treatment. In addition, a patient who objects to treatment is more likely to abandon the plan than a patient who agrees with the medication and acknowledges its effect.
A history of aggressive behaviours and trauma and/or abuse in childhood were new correlates found in the review. Spidel et al [42] suggest that patients with history of the kinds mentioned may be at greater risk of noncompliance with treatment because they have a more restricted level of social functioning. This restricted level may be the result not only of avoiding social situations, which may be stigmatising for the patient, but also greater difficulty trusting others (and in particular health professionals).
Other factors, as in the case of "duration of untreated psychosis", may be relevant to treatment adherence; further research is necessary in this area. The same is true of religious practices, as the only study on the subject included here for review observed that patients who take part in group religious practices at monthly intervals (such as masses, prayer groups and sharing groups) showed rates of treatment adherence that were higher to a statistically significant degree [29]. In the light of this observation, future investigation should focus on this area, to clarify the existence of this relationship and its basis – will it be due to a possible group pressure exercised, or is it due to religious belief *per se*? – as interventions involving the religious context could be designed with a view to optimising patients' treatment adherence.
Among factors related directly to pharmacological treatment, none appeared to influence treatment adherence significantly. Although statistically significant differences in treatment adherence between the two classes of antipsychotic were not observed, the lack of methodological consistency between studies on this point and the asymmetry in sample size under typical and atypical antipsychotics make it impossible to draw conclusions on this topic in particular. In addition, the publications included for review do not permit any conclusions regarding the impact of the advent of prolonged-release medication on treatment adherence; further studies should therefore be conducted in this area. However, it is known that decanoates (prolonged-release antipsychotics) help stabilise the patient, even if an oral dose is missed, reducing the number of clinical relapses and hospital readmissions [63].
The impossibility of drawing conclusions as regards the impact of adverse effects of antipsychotic medication is due to the fact that few studies have focused on this subject and there has been little methodological consistency among those that have (for example, the studies all used different scales for measuring adverse effects). This heterogeneity makes validation difficult and compromises any generalisation that might be made, despite the fact that it is known that up to 70% of patients on antipsychotics experience adverse effects, which may contribute to a decrease in treatment adherence [3, 64]. In practical terms, adverse effects pose an imminent threat of altering the perception of the risk of the antipsychotic medication *versus* its benefit, negatively modifying the patient's attitude to treatment.

It is also important to underline that the reasons that may lead to discontinuation of treatment with each class differ, as the adverse effects associated with each class are different [25, 65]. In this sense, patients have benefited from the development of new antipsychotics, with fewer adverse effects, to limit the potential impact of this factor on treatment adherence.

It is worth mentioning that, although the majority of studies point to a decrease in treatment adherence with adverse effects, some authors state that the occurrence of adverse effects implicitly suggests compliance with the treatment plan. If this is the case, in some cases there may be remission of symptoms and an increase in insight into the disease, which may help patients to stay motivated to stick with the treatment, even if they experience adverse effects [24, 37, 45].

Environment-related factors like the quality of the doctor-patient relationship and social and family support, where present, contribute to better treatment adherence. In the studies included in this review, the overall doctor-patient relationship, to which multiple factors of emotional and cognitive origin contribute, was evaluated. Empathy is reported as one of the decisive factors in the quality of the doctor-patient relationship [66], appears to be of great importance to treatment adherence and has been little studied as yet. For example, in diabetic patients a positive association was observed between the doctor's empathy, treatment adherence and the patient's degree of satisfaction with the doctor [67]. For this reason, there are authors who advocate that empathy should be actively taught and practised on undergraduate medicine courses, as early acquisition of these skills will have direct positive repercussions on the level of empathy that students will show as health professionals [68]. As the majority of the literature in this area focuses primarily on physical conditions, it remains to be clarified whether this individual impact of empathy is verifiable also in adherence to treatment of psychiatric disorders like schizophrenia; this is a point of interest for future investigations. If this relationship is confirmed, interventions seeking to improve the empathy of psychiatrists could make a significant contribution to improving the doctor-patient relationship and levels of treatment adherence.

In this literature review, the stigma associated with mental illness and treatment with antipsychotics was analysed in a small number of articles. However, stigma (and the patient's perception of it) may be a decisive factor in treatment adherence. Stigma affects not only the patient, but also his or her family members and friends, who may have difficulty acknowledging the disorder in front of others, out of fear or shame [69]. For the patient, stigma may have deleterious long-term consequences, resulting in low self-esteem and social isolation; this may have a negative influence on treatment adherence and compromise their recovery [70]. Often the workplace is the place where a patient may be subject to a stigmatising environment created by his or her colleagues; there are indications in the literature that patients with a job tend to hide their treatment from their peers and to take it only in private, to reduce feelings of stigma in relation to their condition [61]. Patients may also anticipate some discrimination from their peers for their actions when they are in the acute phase without treatment (as with the remission of psychotic symptoms and the recovery of insight, patients may gain awareness of their bizarre behaviours during the psychotic phase) and this may actively contribute to social isolation.

Table 1 summarises potential risk factors for nonadherence to treatment according to the literature reviewed.

Table 1. Risk factors for nonadherence to treatment

Risk factors for nonadherence to treatment
Young age
Comorbid substance abuse
Psychotic symptoms present
Lack of insight into disorder and need for treatment
Negative attitudes to treatment and/or low level of treatment satisfaction
Poor quality doctor-patient relationship
Lack of social and family support

This review highlights the importance of not neglecting the problems associated with treatment adherence which, where they exist, should be approached from a holistic perspective, with special emphasis on the patient's subjective experience and on the dimensions of the treatment that the patient values. Often the clinician's priorities do not coincide with the patient's [6]; it is essential to reconcile the patient's concerns and preferences in order to increase the likelihood of treatment adherence. Identification of the patient's priorities may be facilitated by taking the patient's case history carefully.

As antipsychotics are the "therapeutic tool" *par excellence* in schizophrenia, and bearing in mind that the consequences of nonadherence can be disastrous, various strategies have been used to increase patients' treatment adherence [3]. The presence of psychotic symptoms and the absence of insight into their condition are known and reported factors that are decisive to treatment adherence and also have repercussions on building an empathic, trusting doctor-patient relationship. Patients benefit from a treatment plan that includes a full personal rehabilitation plan, making use of psychoeducational and cognitive behavioural interventions as well as occupational therapy. Active involvement of family in this process may be crucial to avoiding relapses [14]. Combining all the relevant decisive factors for an individual in their treatment, to structure a pharmacological, behavioural, family and social approach to the ill-

ness so that they comply with the treatment plan, may be the key to success in stabilising the patient.

This study has a number of limitations that should be mentioned. The current literature on factors that influence treatment adherence in schizophrenia is controversial, because of a lack of methodological coherence and of consensus on many definitions. This leads to a heterogeneity of results that makes it difficult to systematise ideas and interventions. In the first place, some articles relevant to the subject may not have been included, as only publications available in English in PubMed/MEDLINE were included. In the second place, the lack of methodological consistency among the various studies included for review (particularly as regards the definition of treatment adherence and the tools used to evaluate it) may be highlighted as a problem, as it make it difficult to compare data and reach conclusions.

6. Conclusions

In schizophrenia, good adherence to treatment with antipsychotics is essential in order for remission of symptomatology and recovery of insight into the illness to occur. Poor adherence to pharmacological treatment has a negative effect on disease prognosis, as it increases the risk of psychotic episodes and hospital readmissions. With each relapse, symptomatic remission can become increasingly difficult, increasing the risk of the development of residual psychotic symptoms.

In this review, the following were identified as the main risk factors for low treatment adherence in these patients: young age, substance abuse, the presence of psychotic symptoms, absence of insight into the disorder and the need for treatment, negative attitudes to treatment and/or low levels of treatment satisfaction, poor quality doctor-patient relationship and lack of social and family support.

Each patient should be assessed fully and individually for possible factors that may contribute to poor treatment adherence. Identifying these factors will serve as a guide for planning interventions aimed at modifying this behaviour. Particularly prominent are psychoeducational interventions designed to increase the information patients have about their medical condition, and these can be individual or group interventions (including other patients or the patient's family). Involving family in the rehabilitation process is also of great importance for treatment adherence.

The impact of the physician's empathy on treatment adherence has yet to be entirely clarified; further research into this important topic is therefore necessary. Investigation in this area may contribute to the development of new interventions in medical training, in this case reinforcing the clinician's ability to establish a high level of empathy, motivating the patient to comply fully with treatment.

Conflicts of interest: The authors have no conflicts of interest to declare**.**

Sources of funding: The authors had no sources of funding to produce this paper.

Bibliography

1. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med. 2005; 353(5): 487-497.
2. Fleischhacker WW, Oehl MA, Hummer M. Factors influencing compliance in schizophrenia patients. J Clin Psychiatry. 2003; 64(SUPPL. 16): 10-13.
3. Velligan DI, Weiden PJ, Sajatovic M, et al. The expert consensus guideline series: Adherence problems in patients with serious and persistent mental illness. J Clin Psychiatry. 2009; 70 Suppl 4: 1-46; quiz 47-8. doi:http://dx.doi.org/10.4088/JCP.7090su1cj
4. Weiden PJ. Redefining medication adherence in the treatment of schizophrenia. Psychiatr Clin North Am. 2016;39(2):199-216. doi:10.1016/j.psc.2016.01.004
5. Day J, Bentall R, Roberts C, et al. Attitudes toward antipsychotic medication: The impact of clinical variables and relationships with health professionals. Arch Gen Psychiatry. 2005; 62(1): 717-724. http://archneur.jamanetwork.com/article.aspx?articleid=208728.
6. Fenton WS, Blyler CR, Heinssen RK. Determinants of medication compliance in schizophrenia: Empirical and clinical findings. Schizophr Bull. 1997; 23(4): 637-651.
7. Lacro JP, Dunn LB, Dolder CR, et al. Prevalence of and risk factors for medication nonadherence in patients with schizophrenia: a comprehensive review of recent literature. J Clin Psychiatry. 2002; 63(10): 892-909. doi:http://dx.doi.org/10.4088/JCP.v63n1007
8. Sendt KV, Tracy DK, Bhattacharyya S. A systematic review of factors influencing adherence to antipsychotic medication in schizophrenia-spectrum disorders. Psychiatry Res. 2015; 225(1): 14-30. doi:10.1016/j.psychres.2014.11.002
9. WHO. Defining Adherence.; 2003. www.who.int/chp/knowledge/publications/adherence_report/en/?
10. Cramer J, Rosenheck R. Compliance with medication regimens for mental and physical disorders. Psychiatr Serv. 1998; 49: 196-201.
11. Organization WH. WHO Factsheets – Schizophrenia. http://www.who.int/news-room/fact-sheets/detail/schizophrenia.
12. Zygmunt A, Ph D, Olfson M, Boyer C a, Mechanic D. Interventions to improve medication adherence in schizophrenia. Am J Psychiatry. 2002; 159(7): 1653-1664. doi:10.1176/appi.ajp.159.10.1653

13. Mullins CD, Obeidat NA, Cuffel BJ, Naradzay J, Loebel AD. Risk of discontinuation of atypical antipsychotic agents in the treatment of schizophrenia. Schizophr Res. 2008; 98(1-3): 8-15. doi:10.1016/j.schres.2007.04.035
14. Figueira ML, Sampaio D, Afonso P. Manual de Psiquiatria Clínica. (Lidel, ed.). Lisbon; 2014.
15. Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for the treatment-resistant schizophrenic – a double-blind comparison with chlorpromazine. Arch Gen Psychiatry. 1988; 45.
16. Bhanji NH, Chouinard G, Margolese HC. A review of compliance, depot intramuscular antipsychotics and the new long-acting injectable atypical antipsychotic risperidone in schizophrenia. Eur Neuropsychopharmacol. 2004;14:87-92. doi:10.1016/S0924-977X(03)00109-3
17. Higashi K, Medic G, Littlewood KJ, Diez T, Granström O, De Hert M. Medication adherence in schizophrenia: factors influencing adherence and consequences of nonadherence, a systematic literature review. Ther Adv Psychopharmacol. 2013; 3(4): 200-218. doi:10.1177/2045125312474019
18. Bodén R, Brandt L, Kieler H, Andersen M, Reutfors J. Early non-adherence to medication and other risk factors for rehospitalization in schizophrenia and schizoaffective disorder. Schizophr Res. 2011; 133(1-3): 36-41. doi:10.1016/j.schres.2011.08.024
19. Rittmannsberger H, Pachinger T, Keppelmüller P, Wancata J. Medication adherence among psychotic patients before admission to inpatient treatment. Psychiatr Serv. 2004; 55(2).
20. Puschner B, Born A, Giebler A, et al. Adherence to medication and quality of life in people with schizophrenia. Results of a European multicenter study. J Nerv Ment Dis. 2006; 194(10): 746-752 7p. doi:10.1097/01.nmd.0000243082.75008.e7
21. Byerly MJ, Nakonezny PA, Lescouflair E. Antipsychotic medication adherence in schizophrenia. Psychiatr Clin North Am. 2007; 30(3): 437-452. doi:10.1016/j.psc.2007.04.002
22. Bressington D, Mui J, Gray R. Factors associated with antipsychotic medication adherence in community-based patients with schizophrenia in Hong Kong: A cross sectional study. Int J Ment Health Nurs. 2013; 22(1): 35-46. doi:10.1111/j.1447-0349.2012.00830.x
23. Sweileh WM, Ihbesheh MS, Jarar IS, et al. Antipsychotic medication adherence and satisfaction among Palestinian people with schizophrenia. Curr Clin Pharmacol. 2012; 7(1): 49-55. doi:10.2174/157488412799218761
24. Kao YC, Liu YP. Compliance and schizophrenia: The predictive potential of insight into illness, symptoms, and side effects. Compr Psychiatry. 2010; 51(6): 557-565. doi:10.1016/j.comppsych.2010.03.007
25. Novick D, Haro JM, Suarez D, Perez V, Dittmann RW, Haddad PM. Predictors and clinical consequences of non-adherence with antipsychotic medication in the outpatient treatment of schizophrenia. Psychiatry Res. 2010; 176(2-3): 109-113. doi:10.1016/j.psychres.2009.05.004
26. Quach P Le, Mors O, Christensen TØ, et al. Predictors of poor adherence to medication among patients with first-episode schizophrenia-spectrum disorder. Early Interv Psychiatry. 2009; 3(1): 66-74. doi:10.1111/j.1751-7893.2008.00108.x
27. Gianfrancesco FD, Rajagopalan K, Sajatovic M, Wang R hua. Treatment adherence among patients with schizophrenia treated with atypical and typical antipsychotics. Psychiatry Res. 2006; 144(2-3): 177-189. doi:10.1016/j.psychres.2006.02.006
28. Hui CLM, Chen EYH, Kan CS, Yip KC, Law CW, Chiu CPY. Anti-psychotics adherence among out-patients with schizophrenia in Hong Kong. Keio J Med. 2006; 55(1): 9-14. doi:10.2302/kjm.55.9
29. Borras L, Mohr S, Brandt PY, Gilliéron C, Eytan A, Huguelet P. Religious beliefs in schizophrenia: Their relevance for adherence to treatment. Schizophr Bull. 2007; 33(5): 1238-1246. doi:10.1093/schbul/sbl070
30. Hill M, Crumlish N, Whitty P, et al. Nonadherence to medication four years after a first episode of psychosis and associated risk factors. Psychiatr Serv. 2010; 61(2): 189-192. doi:10.1176/appi.ps.61.2.189
31. Janssen B, Gaebel W, Haerter M, Komaharadi F, Lindel B, Weinmann S. Evaluation of factors influencing medication compliance in inpatient treatment of psychotic disorders. Psychopharmacology (Berl). 2006; 187(2): 229-236. doi:10.1007/s00213-006-0413-4
32. Jónsdóttir H, Opjordsmoen S, Birkenaes AB, et al. Predictors of medication adherence in patients with schizophrenia and bipolar disorder. Acta Psychiatr Scand. 2012; 127(1): 23-33. doi:10.1111/j.1600-0447.2012.01911.x
33. Kamali M, Kelly BD, Clarke M, et al. A prospective evaluation of adherence to medication in first episode schizophrenia. Eur Psychiatry. 2006; 21(1): 29-33. doi:10.1016/j.eurpsy.2005.05.015
34. Tunis SL, Faries DE, Stensland MD, Hay DP, Kinon BJ. An examination of factors affecting persistence with initial antipsychotic treatment in patients with schizophrenia. Curr Med Res Opin. 2007; 23(1): 97-104. doi:10.1185/030079907X162665
35. Roberts DL, Velligan DI. Medication adherence in schizophrenia. Drug Discov Today Ther Strateg. 2012; 8(1-2): 11-15. doi:10.1016/j.ddstr.2011.10.001
36. Adelufosi AO, Adebowale TO, Abayomi O, Mosanya JT. Medication adherence and quality of life among Nigerian outpatients with schizophrenia. Gen Hosp

Psychiatry. 2012; 34(1): 72-79. doi:10.1016/j.genhosppsych.2011.09.001
37. Baloush-Kleinman V, Levine SZ, Roe D, Shnitt D, Weizman A, Poyurovsky M. Adherence to antipsychotic drug treatment in early-episode schizophrenia: A six-month naturalistic follow-up study. Schizophr Res. 2011; 130(1-3): 176-181. doi:10.1016/j.schres.2011.04.030
38. Brain C, Sameby B, Allerby K, et al. Twelve months of electronic monitoring (MEMS®) in the Swedish COAST-study: A comparison of methods for the measurement of adherence in schizophrenia. Eur Neuropsychopharmacol. 2014; 24(2): 215-222. doi:10.1016/j.euroneuro.2013.11.013
39. Lecomte T, Spidel A, Leclerc C, MacEwan GW, Greaves C, Bentall RP. Predictors and profiles of treatment non-adherence and engagement in services problems in early psychosis. Schizophr Res. 2008; 102(1-3): 295-302. doi:10.1016/j.schres.2008.01.024
40. Na E, Yim SJ, Lee JN, et al. Relationships among medication adherence, insight, and neurocognition in chronic schizophrenia. Psychiatry Clin Neurosci. 2015; 69(5): 298-304. doi:10.1111/pcn.12272
41. Puschner B, Born A, Giebler A, et al. Adherence to medication and quality of life in people with schizophrenia: results of a european multicenter study. J Nerv Ment Dis. 2006; 194(10): 746-752. doi:http://dx.doi.org/10.1097/01.nmd.0000243082.75008.e7
42. Spidel A, Greaves C, Yuille J, Lecomte T. A comparison of treatment adherence in individuals with a first episode of psychosis and inpatients with psychosis. Int J Law Psychiatry. 2015; 39:90-98. doi:10.1016/j.ijlp.2015.01.026
43. Staring ABP, van der Gaag M, Duivenvoorden HJ, Weiden PJ, Mulder CL. Why do patients with schizophrenia who have poor insight still take antipsychotics? Memory deficits as moderators between adherence belief and behavior. J Psychiatr Pract. 2011; 17(5): 320-329. doi:10.1097/01.pra.0000405362.95881.48
44. Vassileva I, Milanova V, Asan T. Predictors of medication non-adherence in bulgarian outpatients with schizophrenia. Community Ment Health J. 2014; 50(7): 854-861. doi:10.1007/s10597-014-9697-8
45. Staring ABP, Mulder CL, Duivenvoorden HJ, De Haan L, Van der Gaag M. Fewer symptoms vs. more side-effects in schizophrenia? Opposing pathways between antipsychotic medication compliance and quality of life. Schizophr Res. 2009; 113(1): 27-33. doi:10.1016/j.schres.2009.05.022
46. Beck EM, Cavelti M, Kvrgic S, Kleim B, Vauth R. Are we addressing the «right stuff» to enhance adherence in schizophrenia? Understanding the role of insight and attitudes towards medication. Schizophr Res. 2011; 132(1): 42-49. doi:10.1016/j.schres.2011.07.019
47. Boyer L, Cermolacce M, Dassa D, et al. Neurocognition, insight and medication nonadherence in schizophrenia: A structural equation modeling approach. PLoS One. 2012;7(10). doi:10.1371/journal.pone.0047655
48. Eticha T, Teklu A, Ali D, Solomon G, Alemayehu A. Factors associated with medication adherence among patients with schizophrenia in Mekelle, Northern Ethiopia. PLoS One. 2015; 10(3): 1-11. doi:10.1371/journal.pone.0120560
49. Klingberg S, Schneider S, Wittorf A, Buchkremer G, Wiedemann G. Collaboration in outpatient antipsychotic drug treatment: Analysis of potentially influencing factors. Psychiatry Res. 2008; 161(2): 225-234. doi:10.1016/j.psychres.2007.07.027
50. Novick D, Montgomery W, Treuer T, Aguado J, Kraemer S, Haro JM. Relationship of insight with medication adherence and the impact on outcomes in patients with schizophrenia and bipolar disorder: results from a 1-year European outpatient observational study. BMC Psychiatry. 2015; 15: 189. doi:10.1186/s12888-015-0560-4
51. Brain C, Allerby K, Sameby B, et al. Drug attitude and other predictors of medication adherence in schizophrenia: 12 months of electronic monitoring (MEMS®) in the Swedish COAST-study. Eur Neuropsychopharmacol. 2013; 23(12): 1754-1762. doi:10.1016/j.euroneuro.2013.09.001
52. El-Missiry A, Elbatrawy A, El Missiry M, Moneim DA, Ali R, Essawy H. Comparing cognitive functions in medication adherent and non-adherent patients with schizophrenia. J Psychiatr Res. 2015; 70: 106-112. doi:10.1016/j.jpsychires.2015.09.006
53. I. C, A.A. W, O. S. Does level of care, sex, age, or choice of drug influence adherence to treatment with antipsychotics? J Clin Psychopharmacol. 2009; 29(5): 415-420. doi:10.1097/JCP.0b013e3181b2fced
54. Tsai JK, Lin WK, Lung FW. Social interaction and drug attitude effectiveness in patients with schizophrenia. Psychiatr Q. 2011; 82(4): 343-351. doi:10.1007/s11126-011-9177-z
55. Jaeger S, Pfiffner C, Weiser P, et al. Long-term effects of involuntary hospitalization on medication adherence, treatment engagement and perception of coercion. Soc Psychiatry Psychiatr Epidemiol. 2013; 48(11): 1787-1796. doi:10.1007/s00127-013-0687-x
56. Gasquet I, Tcherny-Lessenot S, Lépine JP, Falissard B. Patient satisfaction with psychotropic drugs: sensitivity to change and relationship to clinical status, quality-of-life, compliance and effectiveness of treatment. Results from a nation-wide 6-month prospective study. Eur Psychiatry. 2006; 21(8): 531-538. doi:10.1016/j.eurpsy.2005.09.014

57. McCabe R, Healey PGT, Priebe S, et al. Shared understanding in psychiatrist-patient communication: Association with treatment adherence in schizophrenia. Patient Educ Couns. 2013; 93(1): 73-79. doi:10.1016/j.pec.2013.05.015
58. Shi L, Zhao Y, Fonseca V, Ascher-Svanum H, Chiang Y-J, Winstead D. Healthcare resource utilization, adherence and persistence with antipsychotic therapy among schizophrenia patients with vs. without preexisting metabolic syndrome. Curr Med Res Opin. 2010; 26(10): 2499-2506. doi:10.1185/03007995.2010.519278
59. Jónsdóttir H, Friis S, Horne R, Pettersen KI, Reikvam Å, Andreassen OA. Beliefs about medications: Measurement and relationship to adherence in patients with severe mental disorders. Acta Psychiatr Scand. 2009; 119(1): 78-84. doi:10.1111/j.1600-0447.2008.01279.x
60. McCabe R, Bullenkamp J, Hansson L, et al. The therapeutic relationship and adherence to antipsychotic medication in schizophrenia. PLoS One. 2012; 7(4). doi:10.1371/journal.pone.0036080
61. Brain C, Sameby B, Allerby K, et al. Stigma, discrimination and medication adherence in schizophrenia: Results from the Swedish COAST study. Psychiatry Res. 2014; 220(3): 811-817. doi:10.1016/j.psychres.2014.10.016
62. Chakraborty A, King M, Leavey G, McKenzie K. Perceived racism, medication adherence, and hospital admission in African-Caribbean patients with psychosis in the United Kingdom. Soc Psychiatry Psychiatr Epidemiol. 2011; 46(9): 915-923. doi:10.1007/s00127-010-0261-8
63. Buckley PF, Schooler NR, Goff DC, et al. Comparison of SGA Oral Medications and a Long-Acting Injectable SGA: The PROACTIVE Study. Schizophr Bull. 2015; 41(2): 449-459. doi:10.1093/schbul/sbu067
64. McCann T V., Boardman G, Clark E, Lu S. Risk profiles for non-adherence to antipsychotic medications. J Psychiatr Ment Health Nurs. 2008; 15(8): 622-629. doi:10.1111/j.1365-2850.2008.01277.x
65. Sapra M, Weiden PJ, Schooler NR, Sunakawa-McMillan A, Uzenoff S, Burkholder P. Reasons for adherence and nonadherence: A pilot study comparing first-and multi-episode schizophrenia patients. Clin Schizophr Relat Psychoses. 2014; 7(4): 199-206. doi:10.3371/CSRP.SAWE.020813
66. Kane GC, Gotto JL, Mangione S, West S, Hojat M. Jefferson Scale of Patient's Perceptions of Physician Empathy: preliminary psychometric data. Croat Med J. 2007; 48(1): 81-86. doi: 10.1177/00131640121971158
67. Markham F, Hojat M, Louis DZ, Markham FW. Physicians' Empathy and Clinical Outcomes for Diabetic Patients. Acad Med. 2011; 86(3): 359-364. doi:10.1097/ACM.0b013e3182086fe1
68. Batt-rawden SA, Chisolm MS, Anton B, Flickinger TE. Teaching empathy to medical students: an updated, systematic review. 2013; 88(8): 1171-1177. doi:10.1097/ACM.0b013e318299f3e3
69. Thornicroft G, Brohan E, Rose D, Sartorius N, Leese M, Study I. Global pattern of experienced and anticipated discrimination against people with schizophrenia: a cross-sectional survey. Lancet. 2009; 373(9661): 408-415. doi:10.1016/S0140-6736(08)61817-6
70. Mestdagh A, Hansen B. Stigma in patients with schizophrenia receiving community mental health care: a review of qualitative studies. 2014: 79-87. doi:10.1007/s00127-013-0729-4