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Profiling of drug adherence among patients with treatment resistant schizophrenia

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Abstract

A review and meta-analysis of studies was conducted that compared the efficacy and tolerability of typical and second-generation antipsychotics for patients and drug adherence with treatment-resistant schizophrenia. A systematic approach to the evaluation and characterization of treatment resistance in schizophrenia has become increasingly important since the introduction of clozapine, risperidone, and olanzapine. Non-adherence is a complex phenomenon, with a wide variety of patterns. From the prescribed medication, the patient might either take lower or higher doses, follow a schedule other than prescribed, completely abandon the treatment or refuse attending regular visits or being admitted to hospital. Furthermore, the pattern may change in different phases of the disease.

Keywords: Treatment Resistant Schizophrenia, Drug Adherence,Consequences, Causes

Introduction

Treatment-resistant schizophrenia (TRS) has been defined as the persistence of symptoms despite ≥2 trials of antipsychotic medications of adequate dose and duration with documented adherence.[1,2] TRS occurs in up to 34% of patients with schizophrenia.[3–5] Although persistent symptoms may be negative or cognitive,1 persistence of positive symptoms is generally one of the defining features of TRS.[6] However, the failure of serial antipsychotic medication trials is not sufficient to define TRS, as other potential causes of persistent symptoms need to be excluded as well. TRS may present from the first episode of psychosis[3,4,7] or may develop later in the disease progression. Later onset of treatment resistance may be preceded by relapses,[8–10] which in part may result from medication nonadherence or discontinuation.[2] However, it is critical to differentiate true TRS from pseudo-resistance (i.e., when a patient appears resistant, but treatment is inadequate rather than ineffective).[8,11]

TRS results from lack of response to adequate exposure to medication with no confounding factors, whereas pseudo-resistance may occur as a result of medication nonadherence, insufficient plasma levels of a medication, inadequate dosage or duration of treatment, misdiagnosis, adverse events of a treatment masking a response, or the presence of confounding psychiatric or medical comorbidities.[8,11,12] Outcomes for patients with treatment resistance may be improved if identification of TRS occurs earlier in the course of disease rather than after a long duration of untreated psychosis.[13,14] Early identification of TRS may allow for early introduction of clozapine, the only approved antipsychotic for TRS.[12,15] There is some evidence suggesting that a trial of clozapine

may be warranted after even one failure of a non-clozapine antipsychotic course of treatment,[16–18] although this requires further research. Up to 60% of patients with treatment resistance will not respond even to clozapine.[6,19]

Although a wide variety of medication augmentation strategies have been tried, there is a lack of strong evidence regarding the efficacy of such strategies; thus, patients with TRS may have limited treatment options.[20,21] Electroconvulsive therapy (ECT) was found to be helpful for some patients with clozapine-resistant schizophrenia.[22,23] There may be underlying biological differences between patients with TRS and patients with treatment-responsive schizophrenia.[24] Current hypotheses for the biological basis of TRS focus on differences in the functioning of dopaminergic pathways (i.e., supersensitivity or hyper-, normo-, or hypodopaminergic schizophrenia) or changes in glutamate or other neurotransmitter pathways. These theories are not mutually exclusive, with several pathways converging and possibly contributing to the neurobiology of TRS. Elucidating the underlying pathophysiology of TRS may aid in better treatment selection and inform development of future treatments.[8,25] Furthermore, additional research identifying biomarkers of clozapine resistance or response is needed, as well as new treatments for clozapine-resistant schizophrenia.

Definition of non-adherence

Non-adherence is a complex phenomenon, with a wide variety of patterns. From the prescribed medication, the patient might either take lower or higher doses, follow a schedule other than prescribed, completely abandon the treatment[26] or refuse attending regular visits or being admitted to hospital [29]. Furthermore, the pattern may change in different phases of the disease at different levels. [35,36]

A major problem emerging in related literature published until recent years involves disagreement in the definition of non-adherence and the criteria for considering it clinically relevant.[32,37] Fortunately, an international consensus document was recently published on adherence to treatment by patients with serious and persistent mental disorders. [42-44] Current criteria for defining non-adherence are: less than 80% of prescribed medication taken or gaps in medication of at least 7 days.[38]

The goal of this review is to examine advances in our understanding of the underlying neurobiology of TRS as it relates to positive symptoms, that is, symptoms that were not responsive to antipsychotic treatment from illness onset or that were previously, but are no longer, responsive to antipsychotic treatment. Treatment-resistant negative and cognitive symptoms are of great clinical relevance, but the underlying pathophysiology mechanisms are not well understood and more research is needed to identify appropriate treatments for these domains; negative and cognitive symptoms, therefore, are not discussed further in this review. This review examines potential neurophysiological and molecular mechanisms of TRS related to positive symptom treatment targets. Connectivity and volumetric data may provide further insight into the neurobiological mechanisms of TRS but are not considered here because they are less likely to be relevant to the development of new pharmacologic treatments.

Non-adherence is a major problem in the treatment of schizophrenia. Its high prevalence, potentially severe consequences

and associated costs make the study of this phenomenon a priority issue. In this article, basic non-adherence concepts of prevalence, consequences, evaluation methods, methodological restrictions of available studies, risk factors and intervention strategies, are reviewed. Studying non-adherence risk factors is a necessary step toward designing adequately oriented intervention strategies. An operative definition of adherence and good knowledge of its evaluation methods are essential to study this phenomenon. Unfortunately, most available studies contain methodological restrictions, especially concerning the evaluation methods, and an agreed operative definition of adherence has only very recently been reached. Knowing non-adherence risk factors, intervention strategies and available evidence on their effectiveness is essential in making treatment decisions in daily clinical practice.

Methods

A major difficulty and restriction of available studies on adherence is the lack of validated evaluation methods. [30,31] Most studies are based on indirect and subjective measurements such as information reported by patients or their relatives, or review of patients' clinical records.[30,32] Only in a few studies the reference standard method was used, namely electronic monitoring with the MEMS device.[33] Additionally, many studies contain methodological deficiencies such as lack of a control group, poor description of the studied sample or unreliable criteria for establishing a definition of adherence.[41]

Result Table

Identified risk factors for non-adherence by patients with schizophrenia

Patient-related risk factors
Sociodemographic factors
Younger and older patients
Male
General clinical factors
Drugs or alcohol consumption
Previous non-adherence
Psychopathological symptoms
Impaired insight
Cognitive deficiency
Delusion of persecution, poisoning or grandeur
Psychotic symptoms
Negative symptoms
Psychological factors: attitudes, beliefs and other subjective aspects
Negative attitude toward the treatment
Negative subjective response to treatment
Regarding the disease as mild and/or perceived minor benefit from treatment
Shame or stigmatization associated with the medication or the disease
Environment-related risk factors
Poor social and familial support
Negative social perception of the disease
Stigmatization
Difficulty accessing healthcare services
Physician-related risk factors

Poor relationship with the therapist
Poor psychoeducation and information to patients and relatives
Poor contact with the therapist
Inadequate planning of the post-discharge period
Treatment-related risk factors
Ineffectiveness against persistent symptoms (psychotic and negative symptoms)
Fear of adverse effects
Complex medication schedule
Poorer adherence to oral than to intramuscular treatments

Discussion

Up to date, short-term treatments based on simple interventions have proven efficient, although results are not consistent across different studies. However, long-term treatments require complex interventions, which have not generally proven efficient.[48]

In a recent expert consensus document on non-adherence by patients with serious or persistent mental illness [38-40] it was recommended that social and pharmacological interventions should be the first line of action.[39] Combined strategies are recommended,[49] focused on specific adherence-related problems[38-40]and maintained in the long term.[50]

Patient-related interventions

There is no universal intervention that is adequate for all non-adherent patients; thus, identifying the cause of non-adherence in every particular patient is the first step toward establishing a suitable intervention strategy aimed at reducing it.[51]

Thus, interventions are indicated such as: improving insight in patients with poor or no awareness of their disease,[32,33] reducing negative attitudes toward medication,[29,52] reducing psychotic symptoms,[29] reducing drug consumption[38] and improving cognitive functions.[32,33,43]

Psychosocial interventions

Current evidence suggests that psychosocial interventions are not effective in improving adherence, when applied only to patients[30] or when attitudinal and behavioral aspects are disregarded.[53] Family-related interventions have proven efficient, especially long-term ones as well as those combining different strategies.[30,49] Unfortunately, studies on the maintenance of their efficacy in the long term are very scarce.[54] In a 2-year prospective study, psychoeducative interventions involving patients and relatives were associated with higher adherence than control, which was maintained all through the 2 years.[55] However, in patients with a first psychotic episode, family support was a predictor of good medication adherence only for a short period of time, since these patients required persistent family support to stay on medication.[44,45] This complex and intensive interventions with an approach based on support and problem solving (e.g., assertive community treatment) appear to improve adherence. However, the required resources often restrict applicability of such interventions.[30]

Physician-related interventions

The first step toward improving adherence consists in promoting physicians' awareness that non-adherence is a problem affecting most patients.[27] Basic recommendations include establishing a good relationship between patient and therapist, dedicating some interview time to evaluate adherence, assessing possible risk factors for non-

adherence and making attempts to modify them, evaluating patient's motivation to take medication and trying to improve it if necessary, and involving relatives whenever possible.[56]

Further recommendations[51] include: performing routine evaluations of adherence, adapting to the patient's needs and allowing the patient to participate in decisions concerning their treatment, promoting effective communication by using the necessary means for the patient to understand the relevant information, accepting that the patient has the right not to take medication (provided that the patient is not disabled and is sufficiently informed), periodically evaluating patient's beliefs and concerns regarding the treatment and offering the necessary information about the disorder and possible therapies.

Pharmacological treatment-related interventions

Atypical antipsychotic drugs were expected to improve adherence, because of their better adverse-effect profiles. However, no consistent findings up to date support better adherence with atypical than with classical oral antipsychotics[30], although methodological restrictions have been found in those studies.[41] Recent studies based on the use of MEMS showed no differences between atypical and classical antipsychotics in terms of adherence by patients during the post-discharge period[46] or outpatients during regular follow-up.[34] Therefore, clinicians are recommended not to consider good tolerance as equivalent to good adherence.

When possible, pharmacological monotherapy is recommended over polytherapy because of simplicity, less adverse effects, lower risk of drug interactions and easier response evaluation.[28] Although this issue has been scarcely studied, using treatment schedules as simple as possible is recommended, since possible cognitive deficiencies of patients with schizophrenia could impair memorization and correct execution of complex schedules.[28]

It is important to explain to the patient what they can and what they cannot achieve with the medication. Unrealistic expectancies may lead the patient to abandon the medication when such expectancies are not fulfilled.[27] Patients should understand and agree with the specific objectives and the therapeutic strategies used to achieve them. Instructions on medications and schedules should be as simple as possible.[27]

A number of advantages have been reported for depot and long-acting injection treatments, such as: resulting in better adherence, providing the clinician with reliable adherence information,[27] facilitating regular contact between the patient and the therapeutic team,[57] being easier to remember than daily oral treatments,[28] providing immediate detection of non-adherence thus facilitating early intervention,[48] preventing antipsychotic drug substitutions due to assumed inefficiency from relapse episodes that are actually caused by non-adherence,[28] allowing the physician to conduct interviews without questioning on medication to those patients that perceive such questioning as surveillance,[28] and preventing the first-pass-through-liver phenomenon.[57] Despite their advantages, such treatments are not currently used to their highest potential.[27] There is the generalized belief that patients will be reluctant to them. However, if the physician takes time enough to explain these treatments to the patients, showing conviction on their effectiveness, most patients will agree to start with them.[27] Authors have reported very high adherence

rates, up to 96%, in patients under depot treatment,[58] 85% with long-acting injected risperidone[47] and 97% with long-acting injection and depot.[33]

Therefore it can be observed that, a significant number of patients with schizophrenia do not respond adequately to an initial antipsychotic trial. As first step within a treatment algorithm for therapy-refractory schizophrenia 'pseudoresistance' should be ruled out (eg, re-evaluation of the diagnosis, comorbidities, compliance and adherence in terms of medication intake, adequate dose and treatment duration, and achievement of sufficient plasma levels). In case of treatment resistance, two strategies that are often used in clinical routine care contain dose increase of the current administered antipsychotic drug (dose escalation, high-dose treatment) and switch to another, new antipsychotic. Although the response rates for both options are generally rather low, we see from the evidence-based perspective a slight advantage of the switching strategy (preferably to an antipsychotic with a different receptor-binding profile) compared to a high-dose treatment. After treatment failures with at least two different antipsychotic drugs, a monotherapy with clozapine is considered to be the treatment option of first choice. At present, pharmacological combination and augmentation strategies cannot be regarded as a generally recommendable evidence-based treatment method. Antipsychotic monotherapy should be preferably sought. In case of combination treatment, it appears more appropriate to combine preferentially two antipsychotics with different receptor-binding profiles. Augmentation of antipsychotics with other agents should be used primarily to treat specific target symptoms.

Conclusion

The roadmap for understanding the pathophysiology of TRS and improving outcomes for patients should focus on developing methods for categorizing this patient group based on features such as the stage of illness when TRS emerges, clinical phenomenology, the response to dopamine antagonists and clozapine, and biomarkers. Two main dopaminergic theories have been proposed to explain TRS. The first proposes that TRS is characterized by normal dopamine function, while glutamate or other pathways contribute to the distinct neurobiology of TRS. The other proposes that dopamine supersensitivity leads to the development of TRS over time. It is important to recognize that these two models are not mutually exclusive. Moreover, they may explain different presentations of TRS, with the normal dopamine hypothesis explaining treatment resistance from illness onset, and the dopamine supersensitivity hypothesis explaining the development of treatment resistance in some patients. There are still many gaps in the understanding of the pathophysiology and pathways leading to the development of TRS.

Closing these gaps may lead to improved treatment options for patients with TRS. Several candidates for the biological mechanism and/or subtypes of TRS have been identified. However, none have been widely replicated to date, and more research is needed to test them in different patient populations and different phases of illness. The likely heterogeneity of pathways into and mechanisms sustaining TRS within this population further complicates research. Given the major health burden of TRS for patients and families and to make significant progress toward these goals, it would be useful if organizations such as the National Institute of Mental Health (NIMH) in the United States and similar funding bodies around the world placed more emphasis and

funding on research into the underlying biology of TRS.

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