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Review article

A systematic review of factors influencing adherence to antipsychotic medication in schizophrenia-spectrum disorders

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ABSTRACT

Adherence to antipsychotics improves outcome in schizophrenia. There is a lack of consensus on which factors most influence adherence behaviour and methodological issues hinder interpretation of existing evidence. A rigorous systematic search designed to identify robustly implicated factors emerging from methodologically rigorous studies narrowed our search to 13 observational studies (total $N=6235$) relating to adherence, antipsychotics and schizophrenia. Studies varied significantly, with reported adherence rates ranging from 47.2% to 95%. Positive attitude to medication and illness insight were the only factors consistently associated with better adherence, while contradictory results were found for socio-demographic characteristics, symptom severity and side effects. Only distinct aspects of the therapeutic relationship and social support in younger patients were related to good adherence. Antipsychotic type or formulation and neurocognitive functioning did not appear to impact medication adherence. Despite greater methodological rigour in determining studies to include in the present systematic review, it remains difficult to guide clinicians in this vital area and most of the work discussed contained small sample sizes. Future research in this field should therefore prioritise prospective study designs over longer periods and larger samples in naturalistic settings, providing a more appropriate and clinically meaningful framework than widely used cross-sectional designs.

Contents

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1. Introduction

The primary treatment of schizophrenia and other schizophrenia-spectrum disorders is antipsychotic medication. There is no consistent evidence for differences in efficacy between older, "typical" or first-generation antipsychotics (FGA) and newer, "atypical" or second-generation antipsychotics (SGA) (Leucht et al., 2009). With the notable exception of clozapine (Chakos et al., 2001; McEvoy et al., 2006), large and influential clinical trials, such as CATIE, CUtLASS or EUFEST have demonstrated that in terms of quality of life both classes cause equally problematic side-effects (Lieberman et al., 2003a, 2003b; Jones et al., 2006; Kahn et al., 2008), though FGAs are typically associated with prominent movement and endocrine effects, while atypical compounds are more commonly linked to metabolic and cardiovascular complications (Arana, 2000; Reynolds and Kirk, 2010; De Hert et al., 2012).

Existing reviews have found mean rates of adherence around 40–60% (Lacro et al., 2002; Nosé et al., 2003), though these range widely in individual studies, with some reporting between 75% and 90% of patients becoming non-adherent within 1–2 years of discharge from hospital (Weiden and Zygmunt, 1997; Mullins et al., 2008). Suboptimal adherence has been linked to longer duration of inpatient treatment, poorer symptomatic outcome and has been identified as the strongest predictor of relapse in patients with a first episode of psychosis (Coldham et al., 2002; Morken et al., 2008; Abdel-Baki et al., 2012; Caseiro et al., 2012). Even gaps in antipsychotic regimina of several days can have a significant impact on relapse risk, particularly in patients with recent onset psychosis (Masand et al., 2009; Subotnik et al., 2011).

Development and implementation of appropriate interventions to improve this has proven challenging (Osterberg and Blaschke, 2005), with debate surrounding even the definition of "medication adherence". A dichotomous distinction of being either adherent or non-adherent has generally been replaced by a view that complete adherence and non-adherence are the two ends of a spectrum (Julius et al., 2009), within which an estimation of the percentage of time over a specific duration that one is adherent can be obtained (Velligan et al., 2006; Roberts and Velligan, 2011). The lack of universally agreed cut-off points hinders evaluation of the literature, though taking medication as prescribed 75–80% of the time has been generally considered an acceptable level of compliance in more recent publications (Velligan et al., 2007; Julius et al., 2009; Velligan et al., 2009).

Generally, two main types of assessment—objective and subjective—have been employed in contemporary adherence literature (Osterberg and Blaschke, 2005). Objective assessments comprise direct measures, such as blood or urine medication levels. Although relatively more reliable, they are also intrusive, expensive and only provide a momentary impression of behaviour (Baumann et al., 2004) in a simplistic "present vs. absent" manner (Morken et al., 2007; Klingberg et al., 2008; Miller et al., 2009), for a behaviour that may vary from day to day observed in the context of a condition that typically lasts years. However, such measures accord the advantage of accounting for individual pharmacokinetic factors such as gender, weight, smoking behaviour and so forth. Direct observation of medication intake is also possible, though this requires more resource-intensive monitoring of research participants and hence, for logistical reasons is rarely utilised in adherence research. Other objective measures include pill counts, which are simpler and popular, though clearly potentially subject to intentional manipulation and unintentional factors, such as the use of more than one pill bottle and accidental elimination of empty bottles (Sajatovic et al., 2010; Velligan et al., 2010a). Electronic monitoring systems, such as the Medication Event Monitoring System (MEMS®), capture the time and frequency of bottle cap openings and have been increasingly used in adherence research. They cannot, however, capture true medication ingestion and may record false data when not used according to instruction, e.g. through leaving caps open for long periods of time (Sajatovic et al., 2010). Electronic pharmacy records have similarly been employed but, again, will not provide information on actual ingestion and adherence (Roberts and Velligan, 2011). Subjective measures remain most commonly used, with an estimated 75% of all relevant literature employing at least one method based on either patient, clinician, or family/carer based information (Velligan et al., 2006). Despite the large number of different instruments for recording subjective measures of adherence and their ease of use, feasibility and cost-effectiveness, evidence for their methodological limitations and restricted clinical relevance has been accumulating. A widespread lack of instrument validation, frequent absence of detailed measurement description in published work as well as questionable predictive validity are well-known problems (Kikkert et al., 2008, 2011). Further, subjective measures are prone to overestimation of adherence, liability to recall bias by patients and close social contacts (Pomykacz et al., 2007; Remington et al., 2007) as well as under-detection of non-adherence by clinicians (Byerly et al., 2005). No single measurement of adherence is therefore without limitation and attempts have been made to combine multiple methods to enhance the quality of evaluation (Garber et al., 2004; Velligan et al., 2010b).

The low rates of optimal adherence have stimulated research into the possible factors underlying such behaviour in an attempt to provide an empirical backbone to the development of adherence-enhancing interventions. However, only a small number of consistent predictors of adherence have been identified to date. Reviews have commonly divided correlates into three categories: patient, environment, and medication-related factors. Amongst patient-related illness characteristics, demographic variables have shown the least consistent pattern of influence on adherence (Fenton et al., 1997; Lacro et al., 2002; Pinikahana et al., 2002; Acosta et al., 2009). Whereas mixed results have been found for shorter illness duration or an earlier stage of illness (Lacro et al., 2002; Pinikahana et al., 2002), higher symptom severity has received stronger support as negatively influencing adherence (Fenton et al., 1997; Marder, 2003; Perkins et al., 2008). Neurocognitive impairments have inconclusively been linked (Lacro et al., 2002; Remington et al., 2007), but subjects with comorbid substance abuse have been found to be less adherent (Fleischhacker et al., 2003; Bhanji et al., 2004; Abdel-Baki et al., 2012). Patients' positive attitudes to medication, perceived benefits of treatment and insight into illness have been rather consistently linked