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Are attitudes towards medication adherence associated with medication adherence behaviours among patients with psychosis? A systematic review and meta analysis

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Abstract
Background Studies have shown patient attitudes to be an important predictor for health related behaviours including medication adherence. It is less clear whether patient attitudes are also associated with medication adherence among patients with psychoses.
Method We conducted a systematic review and meta analysis of the data of studies that tested the association of attitude measures with medication adherence among patients with psychoses. 14 studies conducted between 1980 and 2010 were included.
Results Results show a small to moderate mean weighted effect size ($r^+ = 0.25$ and 0.26 for Pearson and Spearman correlations, respectively).
Conclusions Theory based interventions that target potentially modifiable attitude components are needed to assess the relationship between positive patient attitudes and adherence behaviours among patients with psychoses.

Keywords Medication adherence · Attitudes · Psychoses

Introduction

Failure to adhere to medication is an important issue among all disease groups, with costly implications both for the patient and health service providers. Among patients with psychoses, non-adherence rates are particularly high, with reports ranging from 20 to 89 % [1, 2]. It has been proposed that patients with psychoses lack insight into their illness, and that this influences adherence to medication regimes [3]. Non-adherence to antipsychotic medication may not only enhance distressing symptoms, and the likelihood of relapse but also negatively influence the patients' quality of life and long-term prognosis [4]. Moreover, failure to adhere to prescribed regimens may result in longer and more frequent periods of inpatient care, leading to increases in the overall cost of care [5].

The possibility that more positive patient attitudes towards medication adherence are associated with better adherence behaviours among various populations including patients with psychoses [6] is of interest given that it may be possible to intervene to change attitudes. There is also increasing emphasis placed on patient-reported outcomes (PROs) among patients with psychoses [7], suggesting that a focus on individual's cognitive representations may be relevant to clinical treatment outcomes among this patient population. This perspective coincides with various social cognitive models (SCMs) such as the health belief model (HBM) [8] and theory of planned behaviour (TPB) [9] that assess various cognitive representations (beliefs or attitudes) about health behaviours.

The term 'social cognition models' refers to a group of similar theories that identify cognitive and affective factors as the proximal determinants of behaviour. Key constructs in the HBM include perceived susceptibility and perceived severity with respect to a given health threat. Like the HBM, the TPB assumes that individuals weigh up the costs and benefits of possible future courses of action. The model assumes that the intention or motivation to perform a behaviour (such as medication adherence) is a function of three determinants including attitude towards the behaviour. Attitudes reflect the person's overall evaluation of performing the behaviour and are based on beliefs

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concerning the likely consequences and evaluations of those consequences of performing a particular behaviour. These beliefs include those specified by the HBM. For example, a patient who believes that taking their medication will lead to more positive (than negative) personal consequences will hold a favourable attitude towards the behaviour.

While relatively few studies have utilised social cognitive theories among patients with psychoses (see [10, 11], for exceptions) they have been applied successfully to numerous health behaviours including adherence to medication regimes among patients with urinary tract infections [12], diabetes [13], HIV or AIDS [14] and travellers in malaria regions [15].

Among psychiatric populations, the self reported drug attitude inventory (DAI; [16]), and the observer rating of medication influence (ROMI; [17]) have been predominately utilised to assess patient attitudes towards adherence. Like attitude constructs in the HBM [18] and the TPB [9], these measures assess beliefs about medication adherence including perceived benefits, costs and relapse prevention. Additionally, the ROMI includes aspects of therapeutic alliance, normative beliefs and barriers to treatment.

Patient attitudes towards medication adherence may provide a potentially important target for intervention as they are proposed to be potentially modifiable [9]. However, before the relevance of attitudes for adherence among patients with psychoses can be established, research synthesis is needed to examine (1) the size of the association between attitudes and medication adherence behaviours and (2) the generalisability of the findings across the relevant studies.

In this review, systematic search and meta-analytic techniques were employed to test the hypotheses that positive patient attitudes towards medication will be positively correlated with adherence behaviours among patients with psychoses. Additionally, study quality will be explored as a moderator of the attitude/adherence association.

Method

Searches and inclusion criteria

A three-stage systematic search was undertaken to locate primary research papers relevant to the review. Initial search terms contained adjectives or derivatives of the following 4 terms: 'medication' (e.g. neuroleptic or antipsychotic), 'compliance' (e.g. adherence), 'attitudes' (e.g. subjective response or health beliefs) and 'psychosis' (e.g. schizophrenia or schizo or psychosis) that were combined using a series of Boolean and/or operators and wildcards. These combinations were used to search Medline, Psychinfo and Psych-articles databases between 1980 and 2010. Only English language journals were considered.

Potentially relevant articles were exported into a reference citation manager where titles and abstracts were screened (by MR) for relevance. At stage 2, studies were included only if (a) at least 70 % of the sample were diagnosed as having a psychotic disorder (including schizophrenia, schizo-affective disorder and psychoses), (b) a measure of attitude with established psychometric properties was included (c) attitude was linked bivariately to at least one measure of medication adherence. The effect size r was used as it represents both the direction and strength of associations. Where data was missing, authors were contacted. Papers from which data were extracted are marked with an asterisk in the reference section.

Data coding

The following data were coded from each primary article including (a) reference details; (b) country; (c) sample size and patient diagnoses; (d) attitude measure(s); (e) study design and length of time to outcome; (f) adherence measure(s); (g) effect size estimate in r; (h) internal reliability of the attitude measure(s); (i) internal reliability of the adherence measure(s) where present. Following previous research [19], Pearson and Spearman correlations were analysed independently; the study details of which are presented in Tables 1, 2, respectively.

In order to minimise bias resulting from statistically dependent findings [19], global composite scores were coded wherever available and no more than two associations were extracted from a single study. Where there were more data available, the later outcome i.e. that measured most distant to the attitude measure was extracted. When different values other than r were reported, the following effect size types were converted into r:t, F, X^2 .

Quality criteria

Due to the problems of multiple testing, a global index of study quality was developed. The following criteria and coding were used to assess for each association the quality of the study reporting it: the sample size ($<30 = 0$, ≥ 30 and $<100 = 1$, $\geq 100 = 2$), study design (cross sectional $= 0$ and prospective $= 1$), the conceptual validity of the instrument used to measure attitude (confounded attitude measure $= 0$, 'pure' attitude assessment $= 1$), validity of the adherence measure (no established scale $= 0$, established scale $= 1$), reliability of adherence measure (self reported, by patient or observer $= 0$, combination of patient and observer self reports $= 1$, combination of objective and self reported measures $= 2$, objective

Table 1 Study details of the Pearson correlations

Author(s) and References	Country	Sample size and % with psychosis	Attitude measure(s)	Study design (CR = cross sectional, PRO = prospective) and length of time to outcome	Adherence measure(s)	Effect size estimate *r* and *N*	Reliability of attitude measure(s)	Reliability of adherence measure(s)
Agarwal et al. [25]	UK	78 (100 %)	DAI	CR	Combination of patient and observer rated compliance based on Lin et al. [40]	$r = 0.23$, $n = 76$	Not reported	Not reported
Donohoe et al. [27]	UK	32 (100 %)	DAI	CR	Observer rated using a structured clinical interview (Adams and Howe [41])	$r = 0.62$, $n = 32$	Not reported	Not reported
Haan et al. [29]	Netherlands	119 (100 %)	ROMI, global scale	PRO 5 years	Observer rated compliance, developed by authors	$r = 0.13$, $n = 97$	Not reported	Not reported
Kamali et al. [44]	UK	87 (100 %)	DAI	CR	Observer rated using a structured clinical interview (Adams and Howe [41])	$r = 18$, $n = 66$	Not reported	Not reported
Kapelowicz et al. [11]	America (Mexican–American population)	155 (100 %)	TPB, Attitude construct	CR	Treatment compliance interview (TCI; Weiden et al. [17]) (Patient, relative and treatment provider versions used).	$r = 0.37$, $n = 155$	$\alpha = 0.91$	Not reported
Kelly et al. [31]	USA	107 (72 %)	HBM, Barriers construct	CR	Self reported compliance (9 items) developed by authors	$r = 0.32$[a], $n = 107$	$\alpha = 0.98$	$\alpha = 0.90$
			HBM, Benefits construct			$r = 0.20$, $n = 107$	$\alpha = 0.80$	
Mutsatsa et al. [33]	UK	101 (100 %)	ROMI, compliance items	PRO Maximum 3 weeks	Observer rated compliance, using the compliance rating scale (CRS; Hayward et al. [26])	$r = 0.04$, $n = 101$	Not reported	Not reported
			ROMI, non-compliance items			$r = 0.29$[a], $n = 101$	Not reported	
Tsang et al. [35]	Hong Kong	86 (100 %)	ROMI, compliance items	CR	Observer rated compliance using the Kemp Compliance scale (KCS; Kemp et al. [42])	$r = 0.30$, $n = 86$	Not reported	Single item
			ROMI, non-compliance items			$r = 0.33$[a], $n = 86$	Not reported	
Quach et al. [34]	Denmark	432 (100 %)	ROMI, compliance items	PRO 2 years	Observer rated, based on structured interview with clients, information from primary care-givers as well as examination of patient's medical records	$r = 0.29$[b], $n = 432$	Not reported	Not reported
			ROMI, non-compliance items			$r = 0.13$[b], $n = 432$	Not reported	

DAI drugs attitude inventory, *TPB* theory of planned behaviour, *HMB* health belief model, *ROMI* rating of medication influence

[a] Reversed scored

[b] Converted into *r*

Table 2 Study details for the Spearman correlations

Author(s) and References	Country	Sample size and % with psychosis	Attitude measure(s)	Study design (CR = cross sectional, PRO = prospective) and length of time to outcome	Adherence measure(s)	Effect size estimate r and N	Reliability of attitude measure(s)	Reliability of adherence measure(s)
Cabeza et al. [26]	Spain	60 (100 %)	DAI	CR	Observer rated based on deviation from prescribed medication taking and unjustified missed appointments	$r = 0.46$, $n = 60$	Not reported	Not reported
Dolder et al. [10]	USA	58 (100 %)	DAI	CR	Refill compliance	$r = 0.07$, $n = 58$	Not reported	Not reported
Fialko et al. [28]	UK	277 (100 %)	MARS, Attitude subscale	CR	Observer rated compliance using the compliance item of the Engagement Measure (Hall et al. [43])	$r = 0.10$, $n = 277$	$\alpha = 0.44$	Single item
Hayward et al. [30]	UK	21 (71 %)	AMQ	PRO (variable, 1–2 months after discharge)	Observer rated by doctors responsible for the patients care	$r = 0.58$, $n = 21$	Not reported	Not reported
Kennedy et al. [32]	UK	182 (100 %)	TPB, Attitude construct	CR	The Kemp adherence scale, (KCS; Kemp et al. [42]) Observer rated (key worker)	$r = 0.20$, $n = 182$	$\alpha = 0.7$	Single item
					Drug behaviour scale (DBS; Kennedy et al. [32]). self reported	$r = 0.32$[a], $n = 182$	$\alpha = 0.7$	Not reported

DAI drugs attitude inventory, *TPB* theory of planned behaviour, *AMQ* attitudes to medication questionnaire, *DBS* Drug behaviour scale, *MARS* medication attitude rating scale

[a] Reversed scored

measure = 3), internal reliability of attitude and adherence measures (internal consistency <0.70 or non reported reliability = 0, internal reliability >0.70 = 1). When adherence was measured objectively rather than self reported, internal reliability was assumed to be to adequate. Scores were summed across each item to create an overall quality score, ranging from 0 to 9 with higher scores indicating better study quality. Studies were then allocated to one of three groups, i.e. low (0–3), medium (4–6) and high quality (7–9), a distinction used in other reviews [20].

Inter-rater reliability

All articles were coded by two independent researchers. An initial agreement rate of 89 % across all judgments was obtained and all disagreements were resolved through discussion.

Analytic strategy

Hypotheses were examined in three analytic steps. First, meta-analytic findings for the overall attitude effects were calculated. Second, publication bias was assessed using Duval and Tweedie's trim-and-fill procedure [21]. Third, study quality was explored as a moderator of the attitude/adherence association.

Consistent with accumulating evidence, heterogeneity in effect sizes was expected [22]. Thus, observed correlations were pooled and corrected for sampling error using a random effects model. The mean observed (r^+) correlation and corresponding confidence intervals were also calculated. Heterogeneity between scores was assessed using I^2 and Q statistics. The Q statistic reflects the total amount of variance in the meta analysis while the I^2 value indexes the proportion of variance that is due to between-study differences and unlike the Q statistic, it is not sensitive to the number of studies considered. I^2 values range from 0 to 100 % and it has been suggested that values of 25, 50 and 75 % indicate low, moderate and higher heterogeneity, respectively [23].

Publication of statistically significant results is more probable [24] which increases the likelihood of type 1 errors (and an over estimation of the mean effect size) in meta analysis. In order to examine this potential bias, we applied Duval and Tweedie's [21] 'trim-and-fill' procedure which estimates the number of studies that may be missing due to publication bias, and then imputes these missing studies prior to re-calculating the attenuated effect size. Plots of effect size against inverse standard errors around the mean effect size estimate were used in these analyses. For the moderation analyses, sub-group analysis was performed by grouping the associations by study quality and assessing heterogeneity between groups using the $Q_{between}$ statistic within a random effects model.

Comprehensive Meta analysis, version 2.0 (Biostat; Englewood, NJ, USA) was used for all analyses.

Results

At stage one, the search strategy yielded a total of 641 papers. After scanning abstracts and titles using the specified inclusion criteria, 111 papers were identified as relevant and read in detail. The substantial exclusions at this stage were due to a large number of studies that had not assessed both attitudes towards medication and adherence behaviours. 14 papers [10, 11, 25–36] of the 111 potentially relevant papers were found to meet all inclusion criteria and were included in the review. The search process is summarised in Fig. 1.

The reported studies were conducted in Hong Kong, Spain, Denmark, the Netherlands, the United Kingdom and the United States. The percentage of patients with psychosis varied between 71 and 100 %.

Data description

A total of 19 independent correlations were analysed. Of these, 13 (N = 1,911) were Pearson correlations (r) while 6 were Spearman Rank-order coefficients (rs) (N = 780). Of the Pearson correlations, 8 were coded as poor in quality (N = 1,034) and 5 as moderate in quality (N = 877). There were no associations coded as good in quality. Of the Spearman correlations, 3 associations were coded as poor in quality (N = 519), 2 as moderate in quality (N = 203) and 1 as good in quality (N = 58).

Figures 2, 3 present the meta-analytic results for the Pearson and Spearman correlations, respectively, and include the study details, sample size (N), each study r, the mean weighted (r^+) and 95 % confidence intervals (CIs)

Overall attitude effect for Pearson's correlations

The averaged corrected correlation between attitude and adherence behaviours was r^+ = 0.25, (CIs = 0.18–0.32), $Q(12)$ 29.95, $p < 0.05$. This represents a small-to-medium effect size and as the confidence intervals did not include zero, the null hypothesis was rejected. All of the effects were positive in valence. The Q statistic, and an I^2 statistic of 51.90 % showed a moderate degree of heterogeneity in the effect size across the studies, which indicated the likelihood of moderators [37].

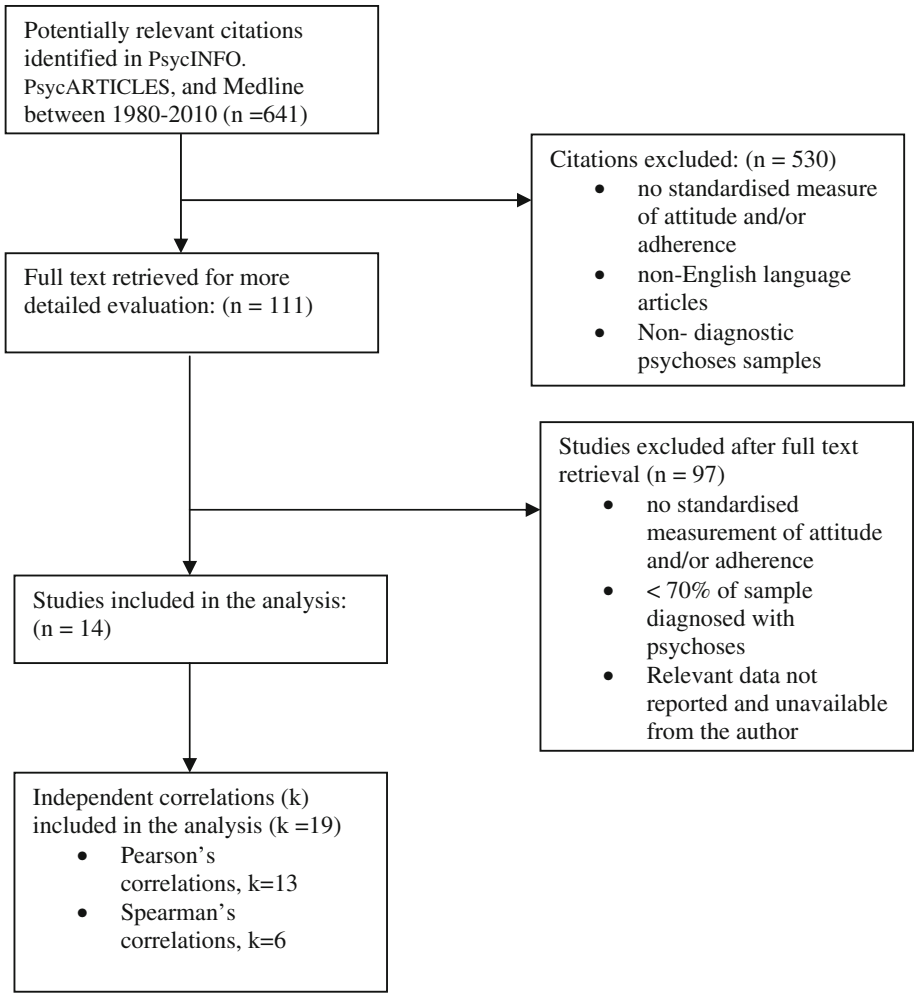
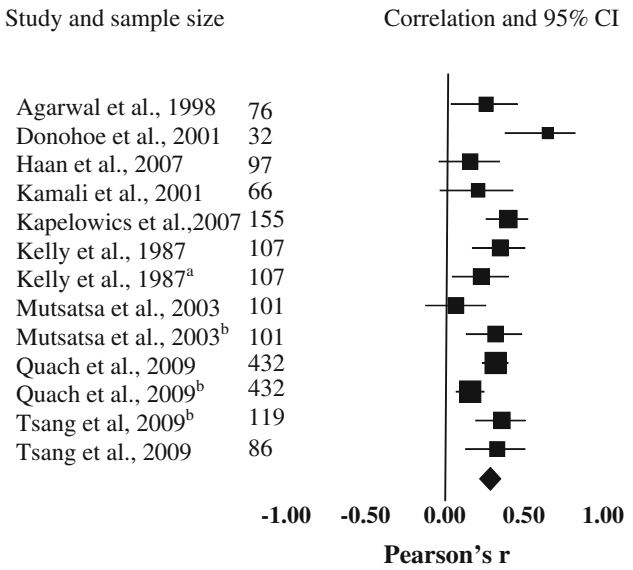
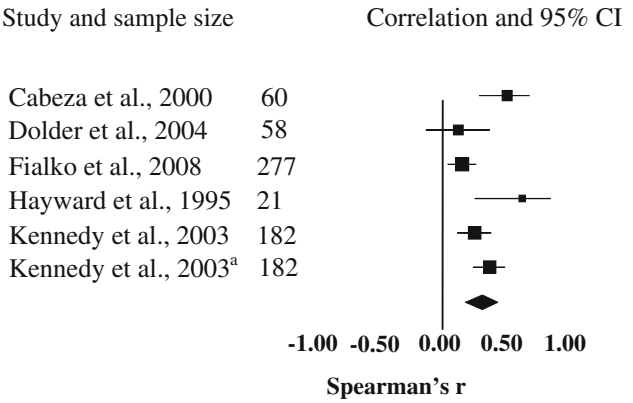


Fig. 1 Search process of the literature



Note : [a] = benefits;[b] = non-compliance items,

Fig. 2 Forest *plot* of the Pearson correlations (with 95 % confidence intervals) between attitude and medication adherence



Note.[a] = drug behaviour scale items

Fig. 3 Forest plot of Spearman correlations (with 95 % confidence intervals) between attitude and medication adherence

Overall attitude effect for Spearman's correlations

The averaged corrected correlation between attitude and adherence behaviours was $r^{+} = 0.26$, (CIs = 0.12–0.38],

$Q(5)$ 15.35, $p = 0.01$. This represents a small-to-medium effect size and as the confidence intervals did not include zero, the null hypothesis was rejected. All of the effects were positive in valence. The Q statistic, and an I^2 statistic of 67.43 % showed a substantial degree of heterogeneity in the effect size across the studies, which indicated the likelihood of moderators [37].

Publication bias

For the overall analyses we found no evidence of publication bias. A single missing effect was identified for the Spearman correlations. However, adjusting for the missing study did not significantly alter the mean effect size (r^+= 0.23, CIs = 0.09–0.36).

Moderator analysis

For the Pearson correlations, sub-group analysis indicated that the between-study heterogeneity was not due to study quality, $Q_{\text{between}} = 1.11$ (1), $p = 0.26$ (for studies coded as medium $r^+ = 0.29$, CIs = 0.19–38; for studies coded as poor, $r^+ = 0.22$, CIs = 0.13–0.30). There were not enough studies using Spearman correlations to explore study quality as a moderator.

Discussion

We systematically reviewed and meta analysed the empirical evidence on attitudes towards medication adherence and medication adherence behaviours among patients with psychoses. A positive relationship of a small to moderate magnitude was observed. However, this should be interpreted in the light of the methodological problems assessing both adherence and attitudes. Study quality as a moderator did not account for the significant heterogeneity between studies. The review has various limitations. Because of the small number of studies we were unable to conduct univariate moderator analysis, which may have explained some of the heterogeneity between studies. Nonetheless, a global index of study quality did not moderate the attitude/adherence combination across the relevant studies suggesting that theoretical moderators may be operating. For example, side-effect profiles may moderate the attitude/adherence association with more noxious medications reducing adherence. It is also important to consider stage of illness (recent onset vs. chronic), patient's psychotic state (active vs. remission) in addition to a number of individual characteristics such as length of illness, substance abuse, gender, ethnicity and social economic status.

The remaining limitations reflect the different ways in which attitudes and adherence are measured and methodological shortcomings of the included studies, only one of which met the defined criteria for a high quality study. There is a considerable body of work showing that measuring attitudes is problematic in some respects. Measuring an attitude rests on the idea that there is one stable underlying concept that can be identified as an attitude towards a particular thing, which may not always be the case. Moreover, there are different conceptualisations of attitudes towards medication operationalised in the various scales used to measure medication attitude in the primary studies reviewed herein. For example, the Medication Adherence Rating Scale includes items on behavioural aspects (forgetting to take medication) and side effects (feeling tired and sluggish). Both the Drug Attitudes Inventory and the Rating of Medication Influences (ROMI) include items relating to subjective experience while on medication. In addition, the ROMI also includes aspects of therapeutic alliance and self-efficacy which although relevant, may be distinctive concepts to patient attitudes. These considerable differences should be kept in mind when interpreting the current findings.

The measurement of adherence is known to be problematic. There is often little agreement about how to define and measure adherence to antipsychotics [2]. Most of the included studies relied on self reports of adherence from either the clinician or the patient, with only one employing an objective measure of adherence. Agreement between different raters can be low. This means that there is likely to be considerable variance in what is being assessed. With respect to psychometric properties of the attitude and adherence scales, internal reliability coefficients were reported in 4 studies for attitudes and a single study for adherence.

The finding that attitudes are small to moderately positively related to adherence behaviour among patients with psychoses is consistent with the findings in other domains and populations, both in direction and size [15] indicating that the patient decision making process is relevant to clinical outcomes among patients with severe mental illness. Thus, despite the specific illness characteristics typically associated with psychoses (e.g. lack of insight) the relationship between attitudes and medication adherence may be comparable to other populations without any mental illness. This finding substantiates recent qualitative reviews [6] and adds to these by providing mean effect size estimates and indexes of heterogeneity. Importantly, this result is consistent with the growing body of evidence indicating that subjective patient reports are associated with clinical outcomes among patients with psychoses [7].

The finding that patient attitudes towards medication adherence are positively related to adherence is consistent with SCMs such as the TPB. The TPB proposes that attitudes predict behavioural intentions, which reflect an

individual's motivation to engage in the behaviour. Following this, patient motivation is the presumed mechanism that accounts for adherence behaviours among patients with psychoses. Nonetheless, the TPB also acknowledges that positive intentions to engage in a behaviour is not always sufficient and self regulatory factors influence the capacity to translate intentions into action. Thus, self regulatory skills such as setting specific plants to implement goals may be needed.

Theoretical models are rarely tested in research on medication adherence among psychiatric populations. This is limiting as theoretical models like the TPB not only specify the causal mechanism of behaviour change but also facilitate the conceptualisation of distinct but closely related constructs [38]. For example, the TPB identifies normative beliefs, and perceptions of control as distinct antecedents of behavioural intention. The current findings indicate that SCMs such as the TPB may be relevant to patients with psychoses although the measures may need to be adapted. Models such as the TPB are often attractive for researchers as additional constructs can be added when they explain variation over and above those already specified in the model. Thus, other constructs (e.g. therapeutic alliance) if found to be relevant could be included.

If these results are replicated in methodologically more sophisticated studies, they suggest that interventions targeting patient attitudes could be developed. An example is the leaflet-like intervention [39] that included persuasive communication targeting the formation of positive attitudes by highlighting the advantages of drinking within daily limits (e.g. fewer headaches and hangovers and lower risk of liver disease). Similar interventions could be developed and evaluated in the context of medication adherence and could have direct implications for healthcare policy and clinical practise. The development of interventions is important because, unlike correlation studies, where only associations are tested, causal statements about the direction of the association can be made in addition to assessments of clinical relevance. A recently developed taxonomy of behaviour change techniques [38] could facilitate the selection of appropriate technique(s) for targeting attitude change and subsequent medication adherence.

This review underlines the need for methodologically more rigorous research and points to at least three requirements for future research in the area. First, attitude and adherence should be assessed with accurate instruments that have been shown to be valid measures among patients with psychosis. Second, research should consider the role of attitudes after consideration of other relevant constructs (e.g. therapeutic relationship), in addition to potential mediating and moderating factors using a theoretical framework such as the TPB. Third, interventions designed to target and improve patient attitudes towards medication adherence should be developed and evaluated.

Medication adherence is a complex issue particularly among patients with psychoses. The evidence reviewed here identifies patient attitudes as central to adherence. Specifically, among patients with psychoses, subjective evaluations of medication adherence appear to be positively related to adherence behaviours. Rational decision making models such as the TPB could therefore be tested empirically among patients with psychoses.

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