



Interventions to improve oral medication adherence in psychosis: the role of adherence measurement

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Practice points

- Among individuals with psychotic disorders, medication nonadherence is widespread, associated with clinical deterioration and difficult to address through intervention.
- When assessing medication adherence in this population clinicians should draw information from multiple sources. In particular, objective sources such as pharmacy records and pill count should be included in assessment.
- Brief interventions and interventions based on one-on-one psychotherapy techniques may be insufficient to enhance adherence.
- There is growing support for interventions that employ concrete problem solving, behavioral and environmental cuing practices.
- For many individuals with psychotic disorders, medication adherence difficulties may result more from cognitive difficulties, such as forgetfulness, rather than from disinclination to take medication.

SUMMARY The benefit of psychotropic medication in the treatment of psychotic disorders depends on patients taking the medication as prescribed. Medication nonadherence is high among individuals with psychotic disorders, leading to substantial disability, relapse and health care costs. The current article reviews the efficacy of interventions to improve adherence with oral medications among individuals with psychotic disorders, paying special attention to the quality of adherence measurement used in the studies. As in previous reviews, most of the 43 studies included in this review used subjective measurement of adherence. Across studies, findings suggest that interventions that do not specifically target medication adherence are unlikely to improve this domain, even if they are delivered in high dosage, such as in case management models. Evidence regarding the benefit of low-intensity interventions that specifically target medication adherence (including cognitive motivational approaches) remains fairly weak. Most positive studies in this category use subjective measurement, which may lead to overestimation of benefit. Finally, newer research suggests that individualized environmental supports delivered through home visits may improve medication adherence. More research is needed using objective measurement approaches, and evaluating lower intensity treatments using environmental supports, behavioral principles and strategic problem solving.

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The advent of antipsychotic medications ushered in a new era in the treatment of psychosis, improving the ability of many individuals with this illness to live independently [1]. However, to receive these benefits, patients must take medications as prescribed. Although medication nonadherence is common across illnesses [2], it is particularly prevalent in schizophrenia, with rates approaching 70% [2,3]. Medication nonadherence in schizophrenia and related psychoses can be devastating to the individual and costly to society, leading to increased emergency room visits and inpatient hospitalizations [4,5].

Numerous treatments have been developed to improve medication adherence in schizophrenia. Reviews of this literature suggest a benefit for targeted over nonspecific interventions, and for behavioral and motivational over purely psycho-educational interventions [6–10]. However, these conclusions have been tempered by the fact that methodological heterogeneity in intervention studies has largely prevented the use of meta-analytic techniques (although see [8]).

In addition to methodological heterogeneity, a key limitation of this literature is the high proportion of studies that do not include objective measures of medication adherence. A 2006 review found that 77% (124 out of 161) of intervention and cross-sectional studies in this area used only subjective or indirect measures of adherence (e.g., self- or clinician report), while direct or objective measures (e.g., pill count or blood plasma level) were used in less than 23% of studies [11]. Similar proportions have been reported specifically within the adherence intervention literature [7]. Such variation in the quality and control of measurement threatens the validity of research findings, as subjective measures tend to be poor estimates of medication adherence [12] and are vulnerable to bias. Subjectivity-based threats to the validity of treatment outcome studies are exacerbated further in trials in which not only patients, but also clinicians and research assessors may harbor bias. For example, a review of the literature on cognitive behavioral therapy (CBT) for psychosis found that studies that used non-blinded assessors systematically recorded larger CBT-related effect sizes than studies which used blinded assessors [13]. Furthermore, the threat of biased self-report may be greater among individuals with psychotic disorders than in other patient groups because psychotic disorders are associated with poor insight [14] and

metacognition [15], which can lead to substantial inconsistency between self-report ratings and ratings made by clinicians or study assessors [16].

A final limitation with this literature concerns the distinction between oral and injectable medication. There is great variation in the logistical and psychological factors that may impact adherence with these two forms of medication. Oral medication requires patients to remain vigilant, attentive, and motivated to take their medications on a daily basis, and to self administer medication. By contrast, injectable medication requires much less vigilance, but typically requires the patient to travel to his or her mental health provider, and requires the patient to tolerate a needle injection. Given these differences in the potential causes of non-adherence, treatments to improve adherence for oral versus injectable medications should be expected to differ systematically in their approach, and may also differ systematically in their effectiveness.

Although four reviews of the literature on treatments to improve medication adherence in psychosis have been published in the past 15 years, none has systematically addressed either the impact of adherence measurement on findings, nor the difference between oral and injectable medication adherence. In light of this, the current study is a focused review of the empirical literature on treatments to improve adherence with oral antipsychotic medication, taking into account the type of medication adherence measurement used. It was hypothesized that studies using subjective measurement of adherence would report greater efficacy than studies using objective measurement.

Method

■ Identification of studies

Studies were identified through PubMed and Medline searches, including the search terms: adherence, compliance, noncompliance, antipsychotic, medication, treatment, intervention, outcome, schizophrenia, schizoaffective, psychosis and psychotic. Reference lists from identified studies and from review articles on treatment adherence in psychosis were also reviewed [6–11].

Studies were selected which met the following criteria:

- English language;
- Published in peer-reviewed journals between 1980 and 2010;

- At least 60% of participants diagnosed with a primary psychotic disorder (studies were excluded if proportion of participants with psychotic diagnosis could not be established);
- At least two distinct treatment groups;
- At least ten participants per treatment group;
- Included a measure of medication adherence as either a primary or secondary outcome;
- No more than 30% of participants were prescribed injectable medication (studies were not excluded if depot/oral status was not indicated).

The initial search process produced 101 studies that were candidates for potential inclusion. A total of 66 of these were excluded after inspection for not meeting full inclusion criteria. The remaining 35 were included in the present review. A total of 8 studies evaluated more than one experimental intervention [17–24]. In these instances, each intervention was treated as a separate case for the purposes of our analysis. Overall, 43 interventions were reviewed.

■ Categorization of interventions

The 43 interventions meeting inclusion criteria were categorized on the basis of whether they used ‘objective’ or ‘subjective’ measurement of adherence. These terms were operationalized to discriminate between studies that were vulnerable to rater bias (subjective) and those that were not vulnerable (objective). Specifically, objective measurement of adherence was defined as the direct recording of pill count, pharmacy record data, blood plasma or urine level, or the judgment of an assessor who was blinded to treatment condition drawing on one or more sources of data. Subjective measurement was defined as patient self-report, significant other report, clinician assessment, or the judgment of an assessor who was not blinded to treatment condition. When adherence was measured using more than one method, and data from multiple methods were distinguishable, data from the more objective measure were included in this review. One study using a blinded rater was categorized as using subjective measurement because the data analyzed by the rater consisted entirely of patient interview [25]. A second study was categorized as using subjective measurement because only a portion of ratings were made by a blinded assessor [26].

After this initial categorization, interventions were subcategorized in several respects. First, they were categorized on the basis of whether medication adherence was a treatment target or a secondary outcome variable. Adherence was considered a treatment target if it was described as such in the methods portion of the research article and/or if the intervention had design elements that explicitly targeted medication adherence and adherence was treated as a primary outcome variable in data reporting. Second, interventions were categorized as low intensity or high intensity on the basis of dosage. Low intensity intervention was defined as fewer than three treatment contacts per month and/or fewer than 12 total contacts. This method was used because these parameters were reported in all studies, and it enabled unambiguous categorization of nearly all interventions. One intervention [27] was categorized as low intensity despite reporting a median of 14 treatment contacts [28] because these contacts were indexed by family member participation and the intervention emphasized family contact over patient contact. Finally, interventions were categorized in terms of whether they were associated with positive or null findings regarding medication adherence relative to a control condition. For each intervention, this rating was made independently by at least two of the current authors. In cases of disagreement, consensus was reached through re-evaluation of the article in question and discussion among raters. One intervention yielded equivocal results (the ‘generic environmental supports’ intervention from [23]) and so was not included in future analyses.

Results

Results of this review are summarized in **Tables 1 & 2**. Of the 42 interventions reviewed, 13 (31%) were evaluated using objective measurement of adherence, while 29 (69%) used subjective measurement. Of the 13 objective-measurement studies, seven (54%) yielded positive results. Three of these used low-intensity interventions that targeted adherence: a behavioral-tailoring and environmental supports intervention [18], a culturally adapted form of behavioral family therapy implemented in a developing country [29], and a nine-session group psychoeducation package [30]. Two interventions used variants of a high-intensity combination of individualized environmental supports and home visits [24]. One study provided

Table 1. Interventions using objective measurement of medication adherence (n = 13).

Low intensity		High intensity	
Positive findings	Null findings	Positive findings	Null findings
Interventions in which medication adherence was a treatment target			
Boczkowski (1985), n = 12, 1a [†] , behavioral, environmental [18]	Battle (1982), n = 20, 4, daily education for 2 weeks [17]	Velligan (2008), n = 37, 1b, environmental, home-based [12]	
Razali (2000), n = 74, 1b, culturally modified behavioral family [29]	Battle (1982), n = 20, 4, two education sessions [17]	Velligan (2008), n = 36, 1b, environmental, home-based [12]	
Seltzer (1980), n = 35, 1a, group education sessions [30]	Boczkowski (1985), n = 12, 1a, education session and materials [18]		
	Brown (1987), n = 15, 1, verbal and written education sessions [49]		
	Merinder (1999), n = 23, 5, family and patient education [50]		
Interventions in which medication adherence was a secondary outcome			
Garety (2006), n = 67, 5, first episode multicomponent treatment [31]		Strang (1981), n = 18, 4, behavioral family therapy [32]	Linszen (1996), n = 37, 5, first episode multicomponent [46]

[†]Number listed after sample size corresponds to adherence measurement technique as follows: 1a: Pill count in office; 1b: Pill count in home; 2: Pharmacy record; 3: Smart pill container; 4: Blood plasma or urine level; 5: Blinded assessor.

a suite of low-intensity services for first-episode psychosis (including medication management, vocational and family coaching, and CBT) [31], and one used high-intensity behavioral family intervention [32].

Eleven of the 29 subjective-measurement studies (38%) reported positive findings. Of these, eight (73%) employed low intensity interventions that targeted adherence. These included a group intervention designed to modify patient attitudes toward medication [33], two interventions using structured problem solving and behavior planning [20,34], one using health education meetings [20], two that combined motivational interviewing and cognitive techniques [26,35], one that combined motivational interviewing with behavioral problem solving [36], and one combining brief counseling and social reinforcement [37]. Positive findings were also reported in a shorter, subjective-measurement replication [23] of the environmental supports and home visits intervention noted earlier [24]. The remaining two subjective-measurement studies that found positive results used high intensity interventions that did not specifically target medication adherence. One was an 18-month intervention that combined individual and multifamily modalities [38], and the other used an assertive community treatment model with heightened intensity and availability of services [39].

Of the 42 interventions, 24 targeted medication adherence, of which 14 (58%) exhibited positive results. Of the 18 interventions for

which medication adherence was a secondary treatment target, only four (22%) yielded positive results.

Overall, the largest number of studies evaluated low-intensity, targeted interventions. Findings in this group were equivocal, with 11 showing positive results and nine showing negative results. There were also a high number of nontargeted high-intensity interventions. Here, a clear preponderance of studies (10 out of 13) yielded null results.

To evaluate the potential role that objective versus subjective adherence measurement may have played in study findings, we compared the proportion of ‘positive’ studies in each intervention category across direct and indirect measures. At the most broad level, the fact that a lower proportion of subjective-measurement studies reported positive results (38%) than objective-measurement studies (54%) indicates that there was not a general bias toward subjective-measurement studies confirming hypothesized support for experimental interventions. Among studies in which medication adherence was a secondary outcome, neither objective-measurement nor subjective-measurement categories included a sufficient number of positive findings to usefully compare proportions. The same holds for high-intensity targeted interventions.

By contrast, a discrepancy was observed among studies of low-intensity targeted interventions. Whereas eight of 12 subjective-measurement studies (67%) reported positive

findings, the opposite pattern emerged among objective-measurement studies, with five of eight (63%) reporting null results.

Conclusion & future perspective

This article aimed to evaluate the literature on treatments to improve oral medication adherence among individuals with psychotic disorders. It was hypothesized that studies using subjective measurement would report stronger support for

the intervention in question than those using objective measurement. The hypothesis was not supported overall, as a lower percentage of interventions evaluated with subjective measurement (38%) yielded positive results than interventions evaluated with objective measurement (54%). However, the hypothesized effect was observed within the large subgroup of low-intensity targeted interventions, where 67% of subjective-measurement studies reported positive

Table 2. Interventions using subjective measurement of medication adherence (n = 29).

Low intensity		High intensity	
Positive findings	Null findings	Positive findings	Null findings
Interventions in which medication adherence was a treatment target			
Guimon (1995), n = 10, 9 [†] , group on negative medication attitudes [33]	Anderson (2010), n = 12, 6, cognitive and motivational [51]	Velligan (2009), n = 36, 6, environmental, home-based [23]	Xiong (1994), n = 34, 7, education and multifamily group [47]
Hudson (2008), n = 173, 9, problem solving and behavioral [34]	Gray (2006), n = 204, 6, cognitive and motivational [41]		
Kelly (1990), n = 101, 6, behavior planning with family [20]	O'Donnell (2003), n = 26, 6, cognitive and motivational [52]		
Kelly (1990), n = 112, 6, goal- and outcome-focused education [20]	Streicker (1986), n = 40, 6, education [53]		
Kemp (1996), n = 25, 9, cognitive and motivational [‡] [35]			
Kemp (1998), n = 39, 9, cognitive and motivational [‡] [26]			
Razali (1995), n = 85, 6, education and behavioral reinforcement [37]			
Staring (2010), n = 53, 8, behavioral and motivational [36]			
Interventions in which medication adherence was a secondary outcome			
	Sellwood (2001), n = 28, 6, family cognitive behavioral [27]	Herz (1996), n = 41, 8, individual and multifamily [38]	Bigelow (1991), n = 25, 6, assertive community treatment [42]
	Solomon (1996), n = 28, 6, family-only group education [22]	Sands (1994), n = 30, 9, assertive community treatment [39]	Bond (1988), n = 84, 8, assertive community treatment [43]
	Solomon (1996), n = 34, 6, family-only consultation [22]		Bond (1989), n = 85, 8, assertive community treatment [44]
	Zhang (1994), n = 41, 6, education, multifamily groups [25]		Bond (1991), n = 31, 6, assertive community treatment [19]
			Bond (1991), n = 23, 6, multifocus group and individual [19]
			Glick (1986), n = 36, 8, partial hospitalization [45]
			Glick (1991), n = 93, 6, inpatient family education and coping [48]
			O'Donnell (1999), n = 39, 9, client-focus case management [21]
			O'Donnell (1999), n = 45, 9, case management and advocacy [21]
[†] Number listed after sample size corresponds to adherence measurement technique as follows: 6: Patient self-report; 7: Significant other report; 8: Treating clinician assessment/report; 9: Nonblinded assessor. [‡] Study samples overlap.			

findings compared with only 37% of objective measurement studies.

The evidence reported here supports several broad conclusions. First, support remains equivocal regarding the potential utility of low-intensity interventions. Second, there is consistent evidence that interventions that do not specifically target medication adherence are unlikely to improve this domain. And third, there is growing support for high intensity, targeted interventions. These conclusions are discussed in detail later.

This report is consistent with previous reviews in finding modest and somewhat equivocal support for medication adherence interventions [6,7,11]. The current findings suggest that this uncertainty is driven primarily by studies of low-intensity targeted interventions. Although the preponderance of all positive findings for adherence interventions are in the area of low-intensity targeted interventions (11 out of 18, or 61%), these positive findings have been reported disproportionately in studies using subjective measurement of adherence. Most studies that have objectively measured the effects of low-intensity targeted interventions have produced null findings. This discrepancy suggests that positive conclusions regarding low-intensity motivational interventions may be inflated by unintentional pretreatment bias among patients and research staff.

Skepticism regarding the benefits of low-intensity targeted interventions is heightened further by the fact that two of the three direct-measurement studies that have reported positive findings are hampered by methodological shortcomings. In one study that used both pill count and blood plasma assay of adherence [30], control participants were recruited from a different unit of an inpatient hospital than experimental participants, and at baseline were significantly more likely to be unmarried, unemployed, of less than high school education, and to live alone. At post-treatment, living alone was significantly related to medication nonadherence. Also blood level data were available from only 39% of the sample at baseline, and in-office pill count data from only 48% post-treatment. Partial in-office pill count data has been associated with over-estimation of adherence [11]. In the second of these three studies [29], it appears that pill count data may have been used only to supplement family-member report, and pill count was only attempted twice over a period of 1 year.

The current findings in this category support the conclusion of previous reviews that brief

educational interventions do not appear to be efficacious [6,7]. However, the current conclusion departs from earlier reviews [6] in suggesting that the use of brief approaches based in cognitive therapy and motivational interviewing does not currently have strong support [40]. However, it is notable that the current conclusion is consistent with a recent large, multisite study that found no benefit from motivational and cognitive approaches [41]. Overall, the support for low-intensity targeted interventions, including those based in cognitive and motivational techniques, remains fairly weak.

The second general conclusion is that interventions that do not specifically target medication adherence are unlikely to be effective. This conclusion has been found previously [6], and is strongly supported by the current review. Of the 18 studies that did not specifically target adherence, only four yielded positive results. It is notable that most of the 14 interventions in this category that found null results failed despite the use of intensive services, including assertive community treatment [19,42–44] and partial hospitalization [45]. Of the three high-intensity programs that reported improved adherence despite not targeting adherence, two incorporated family treatment [32,38], and one used case management services of such intensity that patients often had medication doses administered directly to them, and it was suggested that the intervention may be too expensive to be sustainable [39]. By contrast, the three studies that used elements of case management intervention, such as home visits, in combination with techniques that specifically targeted medication adherence found consistently positive findings [23,24]. One exception to this trend was the positive finding in Garety and colleagues' study of a nontargeted intervention program which, despite being utilized at a relatively lower level of intensity by patients, was equipped with a high-intensity suite of services that were individualized on a case-by-case basis [31]. More research is needed to understand positive adherence findings in this study, especially given that a similar intervention used with a similar (first episode) population elsewhere produced null results [46].

Our final conclusion concerns high-intensity interventions that specifically target medication adherence. Prior to 2008, only one study had been conducted using this approach. Xiong and colleagues administered a family-based intervention targeting medication adherence and other factors to an urban Chinese sample [47]. Based on

significant-other reports, this intervention failed to improve medication adherence. Since 2008, two well-designed objective-measurement analyses and one subjective-measurement study have found that medication adherence can be improved with the use of individually tailored environmental supports sustained by weekly home visits. This approach has been supported at high [24] and moderate (3 months) levels of intensity [23]. This approach converges with low intensity behavioral tailoring and problem-solving interventions, which have both received support [18,34]. Replication of these short-term variants using objective measurement [34] and sufficient sample size [18] are warranted.

This review has several notable limitations. First, the range of comparisons and quality of conclusions were limited by not using meta-analytic techniques. As noted elsewhere [6], future research in this area would do well to standardize methodology to enable quantitative comparison across studies. Similar limitations prevented meaningful consideration of a range of other factors that are likely to moderate or otherwise affect medication adherence, including person-level factors (e.g., level of insight, duration of illness and comorbid conditions), treatment-level factors (e.g., complexity of medication regimen), and environment-level factors (e.g., housing and presence of caregiver). Second, because of this review's focus on the role of subjective bias in adherence measurement, studies were categorized in a manner that does not match the more common direct/indirect measurement convention. This limits the comparability of current results with previous analyses.

Looking forward, the current review has implications for both clinical care and research. Most practicing clinicians and clinical services lack the ability to implement high-intensity interventions to enhance medication adherence. Short of this, clinicians may do well to arrange concrete

supports for patients for whom adherence is hindered by memory, planning and organizational problems. Supports may include provision of pill containers, alarms, laminated signs or behavioral scripts. These patients should not be blamed for their adherence difficulties, and appropriate supports can provide a sense of power and control over their illness management. As appropriate, clinicians may also work with caregivers and family members to ensure use of environmental supports and to facilitate maintenance of a medication schedule. For patients whose low adherence is owing more to disinclination to take medication, motivational and cognitive techniques may be used, but their efficacy remains questionable.

Regarding research implications, support for briefer motivational and cognitive approaches remains equivocal. Given the potential cost-effectiveness of these approaches, larger scale studies that measure medication adherence objectively appear to be warranted. The current review lends further support to previous reviews suggesting lack of benefit from diffuse interventions, even when delivered at a high level of intensity. There is recent support for targeted high-intensity interventions using environmental supports and home visits. There is initial evidence that this type of intervention may be effective when delivered in lower-intensity format, but more research is needed.

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