



A systematic review of interventions to enhance medication adherence in children and adolescents with chronic illness

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ABSTRACT

Introduction Poor medication adherence is common in children and adolescents with chronic illness, but there is uncertainty about the best way to enhance medication adherence in this group. The authors conducted a systematic review of controlled trials examining interventions that aim to improve medication adherence.

Method A comprehensive literature search was undertaken to locate controlled trials that described specific interventions aiming to improve adherence to long-term medication, where participants were aged 18 years and under, medication adherence was reported as an outcome measure, and which could be implemented by individual health practitioners. Studies were reviewed for quality and outcome.

Results 17 studies met inclusion criteria: seven studies examined educational strategies, seven studies examined behavioural interventions and three studies examined educational intervention combined with other forms of psychological therapies. Only two of seven studies reported a clear benefit for education on medication adherence, whereas four of seven trials indicated a benefit of behavioural approaches on medication adherence. One trial reported that combining education with behavioural management may be more effective than education alone. Studies which combined education with other non-medication specific psychological interventions failed to demonstrate a beneficial effect on medication adherence. Only two studies examined adherence-promoting interventions in young people with established adherence problems.

Conclusion These findings suggest that education interventions alone are insufficient to promote adherence in children and adolescents, and that incorporating a behavioural component to adherence interventions may increase potential efficacy. Future research should examine interventions in high-risk groups.

INTRODUCTION

Adherence has been defined as 'the extent to which a person's behaviour corresponds with agreed recommendations from a healthcare provider'.¹ Medication adherence refers to the degree to which the medications taken reflect the prescriber's intention.^{2–3} Poor medication adherence is common, especially in chronic illness,^{1,3,4} and is associated with poorer outcomes.^{3,5,6} Interventions to promote adherence may be effective, although benefits are not consistently demonstrated across studies.⁴

What is already known on this topic

- ▶ Medication adherence is an important predictor of treatment outcomes.
- ▶ Poor medication adherence is common in children and adolescents with chronic illness.

What this study adds

- ▶ In children and adolescents, education interventions alone are insufficient to promote adherence; adding a behavioural component may enhance outcomes but a number of negative studies reinforce the need for more research.
- ▶ No studies have identified effective interventions for young people with established poor adherence.

Most existing reviews of adherence-promoting interventions have focused on adults. However, many young people experience chronic illness^{7–8} and poor medication adherence.^{9–12} Involvement of families in medication routines,^{12,13} and varying developmental capacities of children and adolescents^{11,12,14,15} may influence medication adherence, reinforcing the need to identify interventions with demonstrated efficacy in young people rather than translating findings from adult research.^{9,11}

A review of interventions for children suggests that educational or behavioural interventions may be potentially effective for promoting adherence,¹⁶ but this review excluded studies with negative findings, making it difficult to determine the overall utility of intervention. Educational and behavioural interventions are important as they are able to be implemented by individual health practitioners at various treatment stages. In the current review, we aimed to examine educational and behavioural interventions to promote adherence in young people receiving medication for a chronic illness.

METHODS

Search strategy

An extensive search for published literature was conducted. The following electronic databases

were searched for the period January 1980 to June 2007: Medline (OVID), PsycINFO (OVID), CINAHL (OVID), International Pharmaceutical Abstracts (OVID), the Cochrane Library and Web of Science. Search strategy for OVID databases was: (adherence.ti OR compliance.ti OR concordance.ti) AND (child\$ OR adolesce\$ OR pediatr\$) AND (intervention OR treatment OR trial OR medication). Syntax was adjusted for specific databases. Reference lists were searched for potentially relevant articles.

Inclusion criteria

Criteria for inclusion in the review were: (1) participants aged 18 years and under and were receiving medication for at least 1 month; (2) study described a specific intervention aiming to improve medication adherence; (3) intervention did not involve changing the treatment provided and could be implemented by an individual health practitioner; (4) medication adherence outcomes were specifically reported; and (5) statistical comparisons were conducted for intervention and control group.

Studies were excluded from the review if: (1) participants were aged more than 18 years or insufficient detail was provided to ascertain participant age; (2) duration of pharmacological treatment was less than 1 month; (3) medication adherence outcomes were not reported; (4) the article did not examine a specific intervention; or (5) the study did not utilise a comparison group.

Data extraction

All identified abstracts were manually read for their applicability to inclusion and exclusion criteria. Resources were not available to translate articles written in languages other than English. Potentially relevant articles were then obtained and examined. Articles meeting inclusion criteria were scrutinised to extract the following information: sample characteristics (age range, clinical characteristics, sample size); experimental and control interventions; adherence outcomes and method used to measure adherence. Effect size was calculated for each study. Cohen's *d* was calculated from means and SD.¹⁷ For manuscripts where only proportional data were available, strength of effect was quantified using OR and 95% CI, which were then converted to the equivalent of Cohen's *d*.¹⁸

Study quality was assessed using the Delphi list.¹⁹ This instrument includes items relating to whether randomisation was conducted, whether treatment allocation was blinded, whether participant groups differed at baseline, and whether intention to treat analysis was conducted. Total scores are unweighted and range from 0 (poor quality) to 9 (high quality).

RESULTS

Studies identified

Database and reference searches yielded 2995 abstracts, which yielded 122 potentially relevant articles. Of these, 17 met inclusion criteria and were included in the final review (figure 1). Four articles written in languages other than English were identified via abstract as potentially relevant. One article²⁰ appeared to replicate a study already included in the current review.²¹ One study did not focus on young people,²² and two abstracts contained insufficient information to establish whether they reported on intervention studies.^{23 24}

Delphi scores ranged between 0 and 7 (mean 3.8). No studies blinded the patient or the care provider, and only four studies

attempted to blind outcome assessment. All studies except for two utilised randomisation; one used a quasi-random technique allocating participant pairs to alternate treatments,²⁵ whereas the other did not describe treatment allocation methods.²⁶

Participant ages ranged from 9 months²⁷ to 19 years.^{28–30} Three studies focused on younger children,^{21 27 31} five studies recruited adolescents,^{29 30 32–34} while nine recruited both children and adolescents. The majority of articles (*n*=15) examined interventions in young people with no existing adherence problems. A variety of methods were used to measure medication adherence. Electronic monitoring (using MEMS, an electronic device measuring time and frequency of bottle opening), was used in two studies. Most studies utilised self or parent report of number of tablets taken, medication diaries or general adherence behaviour (*n*=9). Four studies utilised serum or urine concentrations of drug or metabolite, and three studies utilised pharmacy dispensing records.

Education alone

Seven studies examined education interventions compared to treatment as usual.^{21 25 30 31 35–37} Education typically involved providing verbal or written information about the nature of the illness, rationale for treatment and benefits of adherence (table 1). Three studies examined a single education session,^{31 35 37} whereas four studies examined repeated education sessions.^{21 25 30 36}

The largest study²¹ assessed three-monthly education using telephone contact, home visits or physician clinic visits, compared to treatment as usual. At follow-up, positive tests for urinary drug metabolite were reported in 85.0% of those

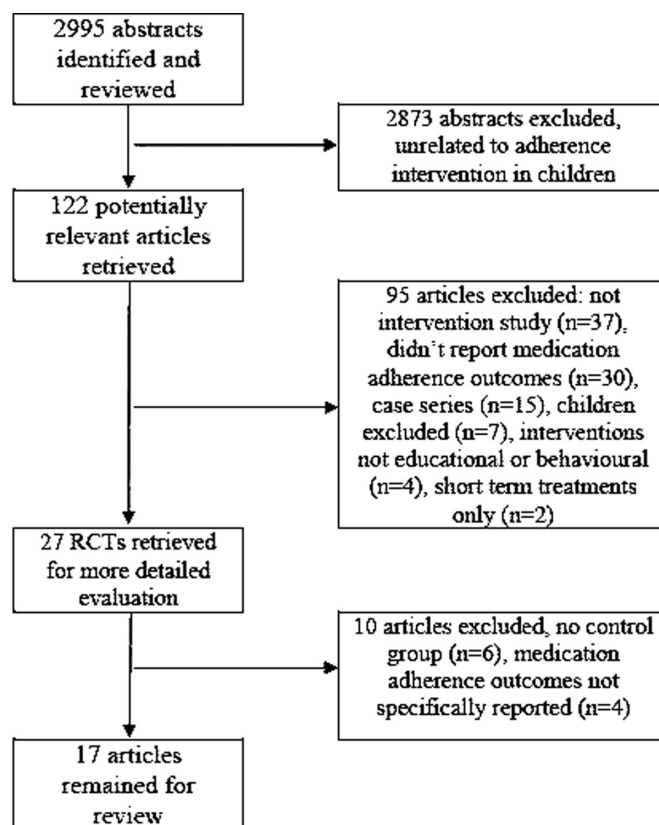


Figure 1 Flow chart of reviewed articles.

Table 1 Trials utilising educational interventions

Study	Age group	Clinical group	No	Intervention	Control	Study period	Adherence measure	Key adherence findings	Delphi score
Salleras Sanmarti <i>et al</i> ²¹	Children (mean age 6.5 years)	Tuberculosis prophylaxis	318	Group 1: Education (verbal) via 3 monthly telephone call by specialist nurses Group 2: Education (written and verbal), via 3 monthly home visits by specialist nurses Group 3: Education (written and verbal) via 3 monthly clinic visits with physician	Usual treatment	12 months	Urine testing for drug metabolite	Groups 1 (d=0.82*), 2 (d=1.08*), and 3 (d=0.46*) superior to control Group 2 superior to group 3 (d=0.62*)	3
Hughes <i>et al</i> ²⁵	Children and adolescents (6–16 years)	Asthma	95	Education: Specialist care and home visits (focusing on overall asthma management in addition to adherence)	Usual treatment (primary care)	12 months	Medication diary	No significant group differences for adherence† Intervention led to better asthma control (d=0.66*)	3
Holzheimer <i>et al</i> ³¹	Children (2–5 years)	Asthma	80	Group 1. Asthma education book and video tape Group 2. Asthma video, control book Group 3. Asthma book, control video	Control book and control video	3 months	Medication diary	No significant group differences†	3
Jay <i>et al</i> ³⁰	Adolescent girls (14–19 years)	Oral contraceptive	57	Education with peer counsellor (four sessions over 4 months)	Education with nurse	4 months	Broad health behaviour scale	Intervention superior to control at 1 (d=0.57) and 2 months (d=0.24) No significant group differences at 4 months (d=0.20)	4
Farber <i>et al</i> ³⁷	Children and adolescents (2–18 years)	Asthma	56	Education (single session, videos and discussion)	Usual treatment	6 months	Dispensing frequency	Adherence was significantly higher in the intervention group compared to control for preventer medication† but not bronchodilators† Intervention group had lower rates of corticosteroid undertreatment (d=0.75*)	6
Berrien <i>et al</i> ³⁶	Children and adolescents (1.5–20 years)	HIV	37	Education—home visits (intensive individualised nursing intervention—8 structured home visits over 3-month period focusing on education and resolving barriers to adherence)	Usual treatment+single home visit if required	3 months	Self report questionnaire and dispensing frequency	Intervention superior to control for self-report questionnaire (d=0.66) and dispensing frequency†	4
Baum <i>et al</i> ³⁵	Children and adolescents (6–16 years)	Asthma	20	Education (single session, 2 hours involving written information, video and discussion on disorder and management) and rewards for completion of forms.	Usual treatment	3 months	Medication diary and blood testing for theophylline	No significant group differences†	1

*Effect size equivalent calculated from OR.

†Data presented in the article do not permit calculation of effect sizes.

receiving education via telephone (OR 4.4; CI 2.09 to 9.59), 89.8% of those receiving education via home visits (OR 7.02; CI 2.97 to 16.55), 74.5% of those receiving education via clinic visits (OR 2.29; CI 1.18 to 4.49), compared to 55.8% in the control group ($p < 0.025$). Another study reported that provision of education within eight structured home nurse visits led to greater adherence based on dispensing frequency than clinic-based education, although group differences in adherence questionnaires were not statistically significant ($p = 0.07$; Cohen's $d = 0.66$).³⁶

Other studies were less clear. In young women receiving the contraceptive pill, adherence scores were better in those receiving education from a peer counsellor compared to a nurse counsellor at 1 and 2 months, but not at 4-month follow-ups.³⁰ Another study in young people with asthma reported that compared to control, a single education session led to improved adherence for inhaled corticosteroids (2.0 vs 0.26 dispensing events over 6 months, $p < 0.001$), but not for bronchodilators (3.70 vs 2.56 dispensing episodes; $p = 0.34$).³⁷

The remaining three studies reported no significant effects on adherence. One study reported fewer non-compliance days in three intervention groups (9.75, 7.62 and 9.08 days compared to 14.87 for control), but this was not significant.³¹ A small pilot study reported that a single session of education did not alter adherence at follow-up.³⁵ Another study reported that home visits focusing on asthma management did not alter adherence, but did reduce asthma severity (OR 3.29; CI 1.07 to 10.13).²⁵

Behavioural management

Seven studies assessed behavioural management, with ($n = 6$) or without ($n = 1$) education (table 2). Behavioural interventions included a range of techniques such as monitoring and goal setting, reinforcing medication taking with rewards, contingency contracting, problem solving and linking medication taking with established routines. Only one study examined behavioural management alone, comparing behavioural management with either self-esteem counselling or treatment as usual. Behavioural management led to significantly greater self-reported number of tablets taken (179.93 \pm 57.01 in the intervention group; 155.37 \pm 69.91 and 150.98 \pm 73.75 in counselling-control and treatment as usual groups).²⁹

Six trials examined combined education and behavioural management. The largest of these³⁸ reported that behavioural management and education led to a significantly greater percentage of asthma medication doses taken (78.0 \pm 2.1%) compared to treatment as usual (54.5 \pm 2.9%). In another asthma cohort, adherence behaviours rated on a 4-point scale increased more in the intervention group (from 1.96 \pm 1.41 to 3.14 \pm 1.16) than control (1.96 \pm 1.35 to 2.14 \pm 1.37).²⁸

Three smaller studies reported unclear findings. A study in children receiving sickle cell prophylaxis reported percentage of medication taken increased from 66.0% to 79.0% in those receiving the intervention, compared to the control group, which decreased from 69.3% to 66.0% ($p = 0.79$).²⁷ A study of children and adolescents receiving anticonvulsants converted serum drug concentrations to a 4-point adherence score (1=non-adherent, 4=excessive adherence).³⁹ When findings were combined for all drugs, adherence scores in those completing the study were 2.9 in the intervention group compared to 2.2 in the control group ($F = 6.36$; $p < 0.05$). This finding was not significant when drug groups were analysed separately or

when all randomised participants were included in the analysis ($F = 3.09$; $p = 0.084$).³⁹ Another study in renal transplant recipients reporting that combined education and behavioural management led to better adherence for one medication (prednisone) but not others (azathioprine, ciclosporin).²⁶

One study using MEMS, reported that proportion of doses taken was significantly higher in patients receiving both education and behavioural management (77.7 \pm 21.5%), compared to those receiving education alone (56.9 \pm 33.0%).⁴⁰ However, no differences were detected in clinical outcomes, making difficult to determine the clinical importance of these findings.

Combined education and psychological interventions

Three studies utilised education in combination with another psychological intervention. In adolescents with depression, education and cognitive behavioural therapy was associated with poorer medication adherence (203.4 \pm 145.8 days of antidepressant medication) compared with treatment as usual (253.5 \pm 191.8 days of medication) ($F = 3.52$; $p = 0.06$).³³ Similarly, education and stress management training in adolescents with diabetes was associated with poorer medication adherence than control.³² Measuring adherence as the difference between time of insulin administration and time recommended via prescription, the first follow-up indicated poorer adherence in the intervention group (65.9 \pm 80.4 minutes) compared to control (24.8 \pm 40.7 minutes), and no group differences at later follow-ups.³² In adolescents with asthma, the combination of education and group therapy led to superior adherence at 24 months, but not at 12 months.³⁴

DISCUSSION

Only two of seven studies reported a clear benefit for education on medication adherence, whereas four of seven trials indicate beneficial effects of behavioural management. One trial reported that combining education with behavioural management may be more effective than education alone. Studies which combined education with other non-medication specific psychological interventions failed to demonstrate a beneficial effect on medication adherence.

Almost all reviewed studies utilised some form of education. Although education provision is an accepted part of clinical practice,¹⁵ many studies failed to demonstrate a clear benefit of education alone on adherence. Positive studies utilised multiple sessions, reinforcing the need to provide information regularly throughout treatment rather than just at treatment initiation.⁴¹ One study also reported a potential role for telephone-based education. The number of negative studies suggest that education, although important, may be insufficient to promote medication adherence. Interestingly, combining education with non-medication specific psychological interventions was not advantageous and in two studies was associated with poorer adherence. Adding psychotherapy to medication may provide an excuse for ceasing medications, exerting a 'treatment offset effect'.³³ Young people receiving psychological therapy may not be protected from poor adherence, and may still require specific interventions to promote medication adherence.

A larger number of studies indicated that behavioural management may enhance adherence. There was no clear relation between intensity or duration of interventions and adherence outcome, making it difficult to recommend specific behavioural approaches. Nonetheless, findings indicate that adding

Table 2 Trials utilising behavioural interventions (with or without education)

Study	Age group	Clinical group	No	Intervention	Control	Study period	Adherence measure	Key adherence findings	Delphi score
Hovell <i>et al</i> ²⁹	Adolescents (12–19 years)	Tuberculosis treatment	286	Behavioural management Monthly meetings incorporating advice about adherence, contingency contracting, problem solving, goal setting, developing routines and family involvement	Group 1: Self-esteem counselling Group 2: Usual treatment	9 months	Missed doses (face-to-face interview)	Intervention superior to both group 1 control (d=0.39, 9 months) and group 2 control (d=0.44, 9 months)	6
Smith <i>et al</i> ²⁸	Children and adolescents (1–16 years)	Asthma	217	Education (written) + behavioural management (linking medication with routines, adherence monitoring)	Usual treatment	9 months	Missed doses (self-report questionnaire)	Intervention superior to control (d=0.93)	4
Bonner <i>et al</i> ²⁸	Children and adolescents (4–19 years)	Asthma	119	Education (group) + behavioural management (symptom monitoring, linking symptoms with patterns of preventer use, action plans, coaching for symptom history detection and reporting, provided by dedicated family worker for 3 months)	Usual treatment	3 months	Perceptions (4 items assessing history of running out of medicines and administration practices)	Intervention superior to control for adherence scores (d=0.79)	4
Shope <i>et al</i> ²⁹	Children and adolescents (<16 years)	Epilepsy, (+/-low drug serum levels)	70	Education (group education for mothers) Behavioural management (verbal commitment for the mother to take active role in managing child's health)	Usual treatment	5 months	Blood testing for drug	Intervention superior to control for per protocol analysis (d=0.81) (trend only for intention to treat, d=0.44)	2
Rapoff <i>et al</i> ⁴⁰	Children and adolescents (2–16 years)	Juvenile rheumatoid arthritis	54	Education (written and verbal) + behavioural management (supported by fortnightly phone contact)	Education (written and verbal, via fortnightly phone contact)	13 months	MEMS	Intervention superior to control for adherence (d=0.75). No significant group differences for clinical outcomes	4
Berkovitch <i>et al</i> ²⁷	Children (9–84 months)	Sickle cell prophylaxis	45	Education (slideshow on disorder and management + behavioural management (calendar with sticker reward system) + home visits (weekly visits by social worker for 2 months)	Usual treatment	6 months	MEMS	No significant group differences after 2-month intervention (d=0.49) or after further 2 months monitoring (d=0.53)	4
Fennell <i>et al</i> ²⁶	Children and adolescents (5–18 years)	Renal transplant	29	Education (booklet, discussion and video). Behavioural management (medication calendar and rewards for adherent behaviour)	Usual treatment	3 months	Blood testing for ciclosporin and pill counts for other drugs	Intervention superior to control for one medication† (prednisone) but not other† (azathioprine and ciclosporin)	0

*Effect size equivalent calculated from OR.

†Data presented in the article do not permit calculation of effect sizes.

Table 3 Trials utilising educational interventions with other psychological intervention

Study	Age group	Clinical group	No	Intervention	Control	Study period	Adherence measure	Key adherence findings	Delphi score
Clarke <i>et al</i> ³³	Adolescents (12–18 years)	Depression	152	Education targeting SSRIs + brief cognitive behavioural therapy (5–9 sessions) for depression	Usual treatment	12 months	Dispensing frequency	Intervention poorer than control for adherence (d=–0.29)	7
Van Es <i>et al</i> ³⁴	Adolescents (11–18 years)	Asthma	112	Education (8 sessions with paediatrician/nurse) + group therapy (3 sessions exploring attitudes, coping skills, peers and cigarette refusal)	Usual treatment	24 months	Self-report, (Likert scale)	Intervention superior to control at 24 months (d=0.46) but not 12 months (d=0.15)	5
Boardway <i>et al</i> ³²	Adolescents (12–17 years)	Diabetes (+ history of poor glycaemic control)	32	Education + stress management training (13 sessions over 6 months, incorporating self-monitoring, problem solving, assertiveness, coping and regimen adherence issues)	Usual treatment	9 months	Time between meal and insulin dose, (24-hour recall interview)	Intervention poorer than control for adherence at 3 months (trend, d=–0.64) and no group differences at later follow-ups (d=0.05 and 0.13)	4

a behavioural component to education may optimise effects on medication adherence. First-line interventions could be selected based on their feasibility and applicability to developmental needs of the child. Interventions for young people with established poor adherence, lack of response to routine interventions or more complicated family issues may require more tailored interventions.

Most reviewed studies, including all studies demonstrating a beneficial treatment effect, utilised participants with no history of poor adherence. As such, these findings are not applicable to young people with established adherence problems. One challenge is that children who are at greatest risk for poor adherence, will also be most difficult to engage in research.⁴² Poor adherence is associated with a variety of risk factors,¹⁵ but data do not indicate how the reason for non-adherence might influence choice of adherence interventions. Ultimately, it remains appropriate to monitor adherence and clinical outcomes throughout treatment, using a stepped approach to interventions when responding to poor adherence.⁴³ Most studies did not examine the role of age in assessing response to adherence interventions. Recommendations typically state that interventions should be targeted to the developmental needs of the child and family. However, little research has focused specifically on this issue, and whether the intervention should target the parent, the child or both.

This review raises a number of questions about improving care. Many primary care professionals could incorporate more regular information provision or simple behavioural techniques into existing practice. In primary care settings, medication information is typically provided by physicians and pharmacists. However, in contrast to adult adherence research,⁴⁴ studies included for review rarely involved pharmacists, and typically relied on nurses, prescribers or researchers. Although the training and skills of health professionals may influence intervention outcomes,^{43 45} it is likely that many members of the multidisciplinary team can contribute to adherence interventions. Multidisciplinary approaches may also facilitate development of new interventions.⁴⁶ One of the challenges for improving outcomes is the

balance between standardised interventions typically used in research settings versus individualised approaches more typical of clinical practice. Further research in this area should consider the capacity for interventions to be implemented by diverse health professionals, and evaluate effectiveness in real-world settings.

This review has a number of limitations. Choice of search terms did not conform to all aspects of Cochrane search criteria. Although we selected terms to strike a balance between sensitivity and precision, it is possible that more sensitive searches would yield additional articles. The quality of studies included for review was typically poor, which is common in adherence research.^{43 44 46} For example, most studies were not adequately blinded. This is logistically difficult in non-drug studies, but does compromise the strength of the positive findings. Many studies did not describe randomisation techniques or power calculations, and did not conduct intention to treat analysis. Many studies also relied on self-report of adherence. Although some adult studies suggest that self-report has similar validity to electronic monitoring,⁴⁷ studies in children suggest that parental self-report leads to overestimation of adherence. Selecting an appropriate control group is also difficult, as monitoring adherence is a core component of behavioural techniques, yet is also an essential component of measuring change in both intervention and control groups. It is possible that measurement of treatment effect may be limited by effect of adherence monitoring in the control group.

CONCLUSIONS

These findings indicate educational interventions alone are unlikely to enhance medication adherence in children and adolescents. Interventions which combined behavioural and educational approaches were more likely to demonstrate beneficial effects, but a number of negative studies reinforce the need for further research. In particular, few data are available to inform best practice for young people with existing adherence problems. Future research should examine those with poor adherence, the relation between efficacy and developmental stage and scope for implementation into practice settings.

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