Author’s response to reviews

Title: Treatment non-adherence in pediatric long-term conditions: systematic review and synthesis of qualitative studies of carers’ views

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Author’s response to reviews: see over
Reviewer 1: Meghan McGrady

Major Compulsory Revisions

Comment 1
Literature Review and Conclusions: While the significance of understanding pediatric adherence is stated, the rationale for conducting a review of the qualitative (versus quantitative) literature remains unclear. The introduction and discussion sections would be strengthened by inclusion of this rationale and integration of qualitative findings with previous quantitative studies in this area (i.e., consistency with quantitative research, how these findings go beyond our knowledge gained from quantitative studies).

Reply
Thank you for these suggestions. We have added the following sentences to the introduction:

Qualitative research is one way of better understanding the views of patients and caregivers. Whereas quantitative research and clinical trials provide strong evidence about mechanisms of adherence and effectiveness of interventions, qualitative research exploring caregivers’ experiences of treatment adherence might offer additional insights. These could inform the development of new interventions or enhance the understanding of clinicians who communicate with families regarding treatment adherence in their everyday practice.

Comment 2
Literature Review: The introduction could be strengthened by including a more extensive literature review targeting pediatric-specific studies.

Reply
Thank you for highlighting this important omission. We have added the references you suggest to the introduction as follows:

Adherence interventions amongst pediatric populations also show that multicomponent interventions are most effective. [Kahana et al 2008, Hood et al 2010] However, the effect sizes are small and inconsistent across studies and settings [Graves et al 2010], effect sizes are small and more research is needed. [Bain-Brickley et al; 2011]

Comment 3
Research Question: The research question remains unclear. The authors state their research question as investigating “reasons for adherence” and “findings that contribute to explaining treatment adherence.” The readability could be enhanced by clarification of the aim (whether the authors were examining “predictors” of adherence, “factors related to adherence,” “the process of adherence,” etc.) and use of consistent language throughout the document.

Reply
Qualitative research is ideal for gaining insights into individuals’ views and experiences but less well suited to examining ‘predictors’ of adherence or ‘factors related to adherence’. In response to Reviewer 2’s comments we have clarified our aim (end of introduction) as:
We therefore conducted a systematic review and synthesis of the qualitative literature to investigate parents and caregivers’ accounts of their reasons for adherence and non-adherence to prescribed treatments in pediatric long-term medical conditions.

Comment 4
Research Question: Related to Comment #3, it remains unclear as to how the authors are conceptualizing the caregiver’s role in adherence. Specifically, the authors state that they are investigating caregivers “reasons for adherence and non-adherence” (page 5). This language may be interpreted as suggesting that the authors are only interested in aspects of adherence that are controlled entirely by the caregiver. As adherence often requires involvement from the caregiver and the child, the authors should consider revising their language to reflect their investigation of “the caregiver-reported factors that influence adherence among youth with a chronic medical condition” (or something similar).

Reply
A review including children’s accounts would indeed be very valuable. But this was beyond the scope of our review, which was already quite ambitious. We acknowledge this as a limitation in the discussion section. We have removed all mention of “families’ views” and replaced these with “caregivers’ views”.

Comment 5
Methods Regarding Study Inclusion: The methods should be clarified to ensure replication and allow for accurate conclusions regarding generalizability. The authors appear to have limited their study to include only articles including children, what age cutoff did the authors use? Did the authors only include studies with an age range within certain limits or with a specific mean age?

Reply
We have changed the final paragraph of ‘Methods – selection criteria’ for greater clarity:

As our focus was on caregiver adherence, included studies had to report on data from caregivers of children aged 12 or younger (studies solely reporting the views of caregivers of teenagers were excluded).

Comment 6
Methods Regarding Study Inclusion: Further, did the authors include only studies examining self-management regimens requiring daily (versus weekly/monthly/etc.) adherence to a recommendation? As adherence is often related to regimen complexity, this clarification is necessary to accurately interpret the results.

Reply
Our selection criteria are described in ‘Methods – selection criteria’ as:

Our focus was on clinical conditions that would widely be viewed as ‘long-term illnesses’. We therefore included conditions such as asthma and diabetes but excluded behavioural, developmental and/or mental health conditions (such as
autism) as well as visual and hearing impairments. Post-operative treatments for long-term conditions were also excluded, for example post-organ transplant. We included studies where caregivers were given specific treatment advice and instructions but excluded studies where general advice was given. So studies reporting on parents delivering physiotherapy in juvenile chronic arthritis were included but not studies where parents were encouraging children with asthma to be more physically active.

All of the papers that met these inclusion criteria were describing adherence to a daily regimen, not weekly/monthly/etc.

Comment 7
Methods Regarding Study Inclusion: While the authors cite that 1996 is the earliest paper published on this subject, use of this rationale requires verification via literature review. Could the authors provide additional justification for this criteria (results of reviews leading to this criteria) or consider altering their rationale (e.g., including articles in the last 15 years)?

Reply
We have altered this rationale to reflect ‘articles in the last 15 years’ as suggested. Qualitative research is not reliably indexed prior to 1996 so it would be difficult to systematically review literature prior to this date.

Comment 8
Methods Regarding Study Inclusion: Can the authors clarify why they excluded “post-operative treatments for long-term conditions?”

Reply
Papers on “post-operative treatments for long-term conditions?” reflected the literature on treatment post-transplant. We have added the following sentence to clarify:

Papers relating to adherence to treatments for the prevention of rejection following organ transplant were also excluded as these formed a substantial number of papers and would have led to an excessive number and heterogeneity of papers.

Comment 9
Methods and Results: CASP Quality Assessment Tool: As some readers may be unfamiliar with qualitative techniques and measures, could the authors provide more information about this measure and how it assesses study quality? Also, the results of this measure appear to be missing from the results section, could the authors please clarify their findings?

Reply
We have added a Table 2 listing CASP criteria and how included papers scored against these.

Minor Essential Revisions

Comment 1
I believe the authors may have made typos in the following text:

a. “published over an 11 year period (1996-2011)” (page 9) – should this say 15 years?

b. “summarized according to five main themes” (page 9) – The authors list 6

Reply
Thank you for pointing out these errors. We have corrected them.

Comment 2
Method: Given the complex inclusion/exclusion criteria, could the authors please provide N’s for studies excluded for: “general advice;” “half the findings” related to adherence, etc.?

Reply
These numbers appear in figure 1.

Comment 3
Discussion: The discussion could be enhanced by discussion of the findings within the context of a larger theoretical model of pediatric adherence.

Reply
We have added the following to our discussion:

The complexity of the processes involved in adherence shown in these studies help to explain the mixed findings from systematic reviews of interventions to promote pediatric treatment adherence (Bain-Brickley et al. 2011). The importance of the ‘fit’ of the treatment regimen with everyday family life helps illuminate the lack of success of interventions that do not attend to the social and family processes involved in treatment adherence (Hood et al. 2010).

Discretionary Revisions

Comment:
Research Question: While the authors included psychological and developmental chronic conditions in their literature search, it appears all included studies examined adherence to a regimen for a chronic medical condition. To enhance the clarity of the manuscript, the authors may wish to consider changing their introduction, title, and discussion to focus specifically on pediatric chronic medical conditions.

Reply
Thank you for the suggestion. We have altered the title accordingly.
Reviewer 2: Scott Burgess

Discretionary points for consideration.

Comment 1
Background 2nd paragraph (page 2). The discussion about the definition could be better expressed. I believe the authors to be arguing that they would prefer to use the terms adherence and compliance as they feel this better reflects the nature of the relationships in the articles reviewed or at least these terms do not presume a degree of negotiation that may not have taken place. It could be read that they don't use the term concordance because they don't agree with the notion of shared decision making which I hope is not the case. Perhaps I have misread the paragraph. Either way I think this could be more clearly expressed.

Reply
We have added the following sentence to the end of this paragraph, in order to clarify: Although shared decision making would ideally occur in all clinical encounters, this cannot be assumed.

Comment 2
Not a recommendation, just a comment. I have not previously read the sentence quoted on the third paragraph page 10 under 1. Carer beliefs, attributed the reference 21. I think this is the best description of this concept I have read and I think the paper is the better for having included it.

Comment 3
Limitations: I think this paper is well written, but I think this methodology has limitations that need to be better discussed. I would suggest the paragraph on limitations be expanded. My argument is as follows: This paper nicely brings together themes discussed by parents with researchers about adherence with treatments. The two main limitations of this concept is (1) Sample and (2) Capacity for insight / social desirability.
(1) Sample. Although the overall sample is good, each individual study is relatively small. The nature of in depth interviews is also going to exclude some clients (mainly as the most non-adherent subjects don't take part in research projects). I run a Difficult asthma clinic in a public hospital. To get into this clinic children have to have poorly controlled asthma despite maximal standard therapy. We monitor adherence with electronic monitoring devices and have a psychologist in our clinic. We have clients who either don't participate in our research group or fail to keep coming to sessions because for multiple reasons, but include significant social disadvantage (for example one boy was taken into foster care and lost to follow-up) and others who come to hospital with acute asthma are very hard to engage. These subjects won't have been captured in such analysis.
(2) The authors have correctly stated that this is analysis of carer's views. But this is not the same as the true reasons (or at least the complete picture) for suboptimal adherence. The two limiting factors are insight and openness. We have clients in our clinic with whom we have been working who have low levels
of adherence but who also have some but limited insight into their own problems. This sounds a little patronising but many of our parents have mental health difficulties or have imitated capacity for in depth reflection. The authors would be aware of the concept of social desirability, a very powerful convention that explains why many parents exaggerate adherence at least a little. The mean adherence in our group at enrolment is 45%, but almost all report 90% plus adherence. A small number of teenagers manipulate their adherence deliberately to ensure their asthma is worse so they miss school. Other parents don’t really know what their children are doing but would not want to report that they have stopped supervising their child. One study found that the degree of supervision reflected their capacity to observe the child and not the child’s maturity. Thus these parent are trying to convince themselves that their child is more mature because they don’t have the capacity to supervise them. Thus it is common for clients to exaggerate adherence and offer more socially acceptable reasons for low adherence. A small number are deceitful because of other agendas including secondary gain.

Reply
Thank you for this comment. It is indeed unfortunate that most research studies include participants where socially disadvantaged groups are under-represented. For qualitative synthesis it is more important to have a diversity of participants than representativeness and some of the studies included here went to some lengths to include socially disadvantaged groups (though not all). We have added the following to the discussion section:

A further limitation is that the participants included in these studies may not have been fully representative of less adherent families in some cases.

The barriers that you relate in the context of asthma did indeed appear in some of the papers included in this study, particularly the finding that parents may not supervise the use of inhalers if social circumstances made this difficult. We did not report them specifically and it is possible that in trying to summarise the data we have lost some of the richness of the factors influencing the balancing act in making a treatment regimen ‘fit’ with family life where that family life may be chaotic.

Comment
Paragraph two under 1. Carers beliefs page 10 is essentially describing the Health beliefs model in which patients weigh the pros and cons of treatments. Whereas my understanding is that human decision making has been more often shown to be based on preconceived notions and split second decisions with such deliberations being more commonly used as post decision rationalisations.

Reply
We completely accept that daily actions may not be nearly as well thought through as post-decision rationalisations described to researchers and accept that carers will wish to present a ‘socially desirable’ position in their accounts. However these deliberations appeared in all studies and, if taken in the context of the other factors limiting treatment adherence, can help to inform our understanding.
Reviewer 3: Mary Irvine

Minor Essential Revisions:

Comment 1
In the Background, the description of related quantitative research (paragraph 3) mentions interventions found to be effective, but does not mention common barriers to adherence identified in this body of literature. Please add a sentence or two, with appropriate citations, about the common barriers identified.

Reply
Thank you for highlighting this. We have added further detail to the introduction, as above.

Comment 2
Also in the Background, the paragraph (4) on qualitative research examining adherence among adults focuses entirely on barriers and does not mention any findings or even recommendations related to strategies for overcoming these barriers. For balance in the literature review, I would suggest adding something about interventions to this paragraph.

Reply
We have added further detail to the introduction, as above.

Comment 3
In the Methods, "Quality of reporting" paragraph, it is somewhat unclear just what was done with the information/assessment on quality of articles. It might help to briefly enumerate the criteria applied (for readers who don't know and may not want to have to review the CASP quality assessment tool). It also seems important to clarify (1) whether _any_ papers were excluded due to quality concerns, and (2) how exactly the use of a paper was affected by its quality scoring, if the paper was retained in the review but judged to be of marginal quality or just of lower quality than some others included.

Reply
We have added table 2 regarding CASP criteria and scoring of the papers included.

Comment 4
In the Results, the mention of an "11-year period" does not match the years shown, which suggest more like a 15-year period of publications.

Reply
Thank you for pointing this out. We have corrected this.

Comment 5
In the "Analytical overview" paragraph just before the Discussion section, the final sentence needs re-tooling, mainly due to multiple clauses lacking separation with commas, and a final clause that refers to "juggling of the balance of..." (I would just go with "juggling" or "balance").
Reply
Thank you – we have adjusted this sentence accordingly.

Discretionary Revisions:

Comment 1
In the first paragraph about "Child resistance" on p. 12, the term "repetitive resistance" could use a bit of definition or explanation. I would have thought that "child resistance" would encompass one-time and (usually) repetitive resistance, and I think explaining the concern of a habit or pattern of resistance that is self-reinforcing, for example, would help to distinguish and make that term more meaningful. But it may just be that I am unused to the term.

Reply
We have added the following to clarify this point:

Some caregivers described a pattern of repetitive resistance, where the child fiercely refused most treatments leading to daily ‘battles’ and caregiver fatigue.

Comment 2
Also in that section on "Child resistance," I thought the example with the quotation (2nd paragraph) was not as clear an example as you'd want. Was there a quotation that gets more at the idea of wanting to let the child have some agency, or not wanting to aggravate the pains of growing up, or having to choose between emphasizing adherence and showing sympathy and support for the child who is having difficulty? I can imagine that the caregiver quoted may have had any or all of those in mind, but it doesn't come across in the statement that the child and the parent are each having a difficult time.

Reply
We are a little bit limited in that some of the papers discussed this concept but presented relatively little data. We have added the following to Box 1 (this is the data excerpt in its entirety):

You end up battling with your child and getting nowhere.[29]

Comment 3
Under either "Child resistance" or "Impact on relationships within families," I was expecting to see some mention of the issues around adherence when the illness is particularly stigmatized, as in HIV, or at least when the illness carries the expectation of a premature death, as in HIV or cystic fibrosis. I would think that would be a major difference between the chronic disease areas included in the review, since stigmatized illnesses and those associated with premature death bring complexities around disclosing the full nature of the illness to the child and (in the case of HIV) addressing the connections between the child's illness and an alternative (foster, adoptive, or extended-family) caregiver arrangement, death or illness of a biological parent, and/or difficult period in a parent's personal history. If issues related to disclosure and addressing premature death were not covered enough in the articles to make that point in the review, then I understand not getting into that. But in my own work related to HIV-related pediatric treatment adherence, issues of stigma and
disclosure were pervasive in management of communications with the child, and an area in which the professional healthcare providers could be particularly helpful, but also could at times come into conflict with the family caregivers (who tended to differ in the direction of protecting children from potentially painful information, when they differed on strategy around disclosing diagnosis and/or its seriousness).

Reply
Fears about premature death in CF are referred to in the section on ‘Carer beliefs about long-term conditions and treatments’. Stigma was indeed an important point in the literature on treatment adherence for HIV and it is unfortunate that this was cut out in our attempt to summarise a great deal of data. We have added the following to the section on ‘preserving normal life’:

This [administering treatment] was particularly problematic for caregivers of children with HIV, who reported difficulties giving treatment to children in front of others who were unaware of their child’s HIV status, due to the perceived stigma of the condition.[26]

Comment 4
I noticed that "regime" was sometimes used interchangeably with "regimen," in places where I think the meaning fit better with "regimen."

Reply
We have corrected this.
Reviewer 4: Ruth Jepson

Comment 1. Are the questions clear?
The questions posed by the researchers are relatively clear, but could do with some further explanation as to why conditions such as arthritis and cystic fibrosis were included but conditions such as autism or behavioural problems were not.

Reply
We have altered the title of the review to include the term ‘pediatric long-term medical conditions’ to make it clear that we are not reviewing the literature on developmental or psychological conditions.