Understanding Patients’ Adherence-Related Beliefs about Medicines Prescribed for Long-Term Conditions: A Meta-Analytic Review of the Necessity-Concerns Framework

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Abstract

Background: Patients’ beliefs about treatment influence treatment engagement and adherence. The Necessity-Concerns Framework postulates that adherence is influenced by implicit judgements of personal need for the treatment (necessity beliefs) and concerns about the potential adverse consequences of taking it.

Objective: To assess the utility of the NCF in explaining nonadherence to prescribed medicines.

Data sources: We searched EMBASE, Medline, PsycInfo, CDSR/DARE/CCT and CINAHL from January 1999 to April 2013 and handsearched reference sections from relevant articles.

Study eligibility criteria: Studies using the Beliefs about Medicines Questionnaire (BMQ) to examine perceptions of personal necessity for medication and concerns about potential adverse effects, in relation to a measure of adherence to medication.

Participants: Patients with long-term conditions.

Study appraisal and synthesis methods: Systematic review and meta-analysis of methodological quality was assessed by two independent reviewers. We pooled odds ratios for adherence using random effects models.

Results: We identified 3777 studies, of which 94 (N = 25,072) fulfilled the inclusion criteria. Across studies, higher adherence was associated with stronger perceptions of necessity of treatment, OR = 1.742, 95% CI [1.569, 1.934], \( p < 0.0001 \), and fewer Concerns about treatment, OR = 0.504, 95% CI: [0.450, 0.564], \( p < 0.0001 \). These relationships remained significant when data were stratified by study size, the country in which the research was conducted and the type of adherence measure used.

Limitations: Few prospective longitudinal studies using objective adherence measures were identified.

Conclusions: The Necessity-Concerns Framework is a useful conceptual model for understanding patients’ perspectives on prescribed medicines. Taking account of patients’ necessity beliefs and concerns could enhance the quality of prescribing by helping clinicians to engage patients in treatment decisions and support optimal adherence to appropriate prescriptions.

Introduction

Prescribing medicines is fundamental to the medical management of most long-term conditions. However, approximately half of this medication is not taken as directed, representing a failure to translate potentially effective treatment into optimal outcomes for patients and society [1,2]. Where prescriptions are appropriate, this level of nonadherence has potentially serious consequences,
both for individual patients, in terms of lost opportunities for health gain with increased morbidity and mortality [3], and for the health care system, in terms of wasted resources, increased use of services and hospital admissions [4].

In the absence of a single definitive intervention to address nonadherence [5], the NICE Medicines Adherence Guidelines amalgamate insights from trials of interventions and explanatory studies of nonadherence [1]. They apply a perceptions and practicalities approach [4] recognizing that nonadherence may be both unintentional and intentional. Unintentional nonadherence occurs when the patient wants to adhere but is unable to because they lack capacity or resources. For example, they may not have understood the instructions, cannot afford copayment costs, or find it difficult to schedule, administer or remember the treatment. Intentional nonadherence occurs when the patient decides not to follow the recommendations. It is best understood in terms of the perceptual factors (e.g. beliefs and preferences) influencing motivation to start and continue with treatment.

Prescribing consultations do not occur in a vacuum. Patients (and prescribers) bring pre-existing beliefs about the illness and treatment [6,7] which influence the patient’s evaluation of the prescription, their adherence and even beneficial [8] or adverse outcomes [9]. Interventions to optimise adherence tend to be more effective if they are tailored to the needs of the individual taking account of the perceptions of the treatment as well as practical abilities and resources that enable or impede their adherence [10]. Although the perceptual and practical dimensions of adherence are influenced by the social, cultural, economic and healthcare system contexts, taking account of the patient’s beliefs about the prescribed medication is fundamental to shared-decision making and supporting adherence [1,11].

Research conducted with patients with a variety of long-term conditions suggests that the key beliefs influencing patients’ common-sense evaluations of prescribed medicines can be grouped under two categories: perceptions of personal need for treatment (Necessity beliefs) and Concerns about a range of potential adverse consequences [7,12,13]. This ‘Necessity-Concerns Framework (NCF)’ potentially offers a convenient model for clinicians to elicit and address key beliefs underpinning patients’ attitudes and decisions about treatment.

Over the past decade, a number of studies have been conducted, using a validated questionnaire, the Beliefs about Medicines Questionnaire [14] to quantify Necessity beliefs and Concerns in order to explore the relationship between these beliefs and adherence. This research spans a range of long-term medical conditions, across different settings and within various cultural groups. Many of the individual studies have demonstrated the utility of the NCF in explaining nonadherence to medication (e.g. [15–18]). It is therefore timely that a meta-analysis is performed to consolidate the results from these studies and to examine the explanatory value of the NCF in predicting adherence to medication prescribed for long-term medical conditions. In line with the underlying theory, we hypothesized that adherence in long-term conditions would be associated with stronger perceptions of Necessity for treatment and fewer Concerns about adverse consequences.

Methods

This review was conducted in line with the MOOSE guidelines for meta-analysis of observational trials [19].

Literature Search

A computerised literature search was conducted by the investigators on April 22nd, 2013 using EMBASE, Medline, PsycInfo, CDSR/DARE/CCT and CINAHL. The search strategy included the following terms:

- **BMQ or belief**
- treatment$ or medicine$ or medication$
- and
- adheren$ or complian$

The search was limited to studies published from the year 1999 onwards (the year in which the BMQ was published). Duplicates were removed.

Inclusion and Exclusion Criteria

Identified studies were included in the meta-analysis if they met the following criteria:

1. participants were suffering from a long-term condition
2. participants were taking medication
3. participants were adults
4. the article was published in a peer-reviewed journal
5. the Necessity and/or Concerns subscales of the BMQ were used
6. a measure of adherence was employed

There were no restrictions based on language, or on cultural or geographical factors.

Titles and abstracts were screened for relevance, and the full text of relevant articles was obtained. Data from each article was extracted as described below.

Selection of Results When Multiple Relationships between Beliefs and Adherence Were Reported

Fifteen studies reported multiple associations of beliefs related to different adherence measurements (details reported in Table 1). Where the choice was between adherence measures, the most objective measure was selected for the meta-analysis. Therefore, electronic monitoring of adherence [20] and prescription redemption data [16] were chosen over self-report. Where data was presented for both ‘on demand’ and prophylactic medications, data for the prophylactic medication data were chosen [21,22], for consistency with medications prescribed for other long-term conditions. In studies where cross-sectional and longitudinal data were both available, longitudinal data was used within the analysis [21,23–26]. Where one group provided cross-sectional data at multiple timepoints, the timepoint with the fewest missing data points was selected [27]. If the choice was between two self-report measures of adherence, we used the more commonly used measure. Thus the Morisky Medication Adherence Scale (MMAS) was chosen over the Brief Medication Questionnaire [28] and the ACTG adherence measure was used over the Walsh VAS scale [29]. Where patients within a sample were taking multiple medications and individual associations were provided for each medication [30,31], the mean association was used within the meta-analysis but individual effect sizes are reported in Table 1 to facilitate comparison. Where data on two samples are reported within the same study [32,33] we included both associations within the analysis.

Data Extraction

The following information was extracted from papers onto coding forms: author names, date of publication, the country in which the research was conducted (dichotomized into UK or non-UK), sample size, illness group, sex (% male), mean age, study design (cross-sectional, longitudinal or prospective), the number of...
### Table 1. Summary Data for Included Studies.

| Author and date       | Country | Illness Group      | N    | % male | Mean age (SD) | Study Design | Adherence measure | BMQ (number of items) | OR     | p     |
|-----------------------|---------|--------------------|------|--------|---------------|--------------|-------------------|-----------------------|--------|-------|
| Aakre et al. (2012)   | USA     | Comorbid           | 44   | 45%    | 51.1 (9.3)    | Cross-sectional | 1) Brief Medication Necessity | 5       | 1.467  | 0.523 |
|                       |         | Serious Mental Illness and Type II Diabetes | 102  | 22%    | 40.7 (11.4)   | Cross-sectional | 2) Brief Medication Questionnaire (Hypoglycaemic medication) | 10 item version | 1.670  | 0.172 |
| Aikens et al. (2005)  | USA     | Depression         | 82   | 21%    | 42.9 (10.63)  | Cross-sectional | 1) General adherence: 4- Item MMAS | 5       | 2.097  | 0.075 |
| Aikens & Piette (2009)| USA     | Diabetes           | 803  | 38%    | 55.3 (11.8)   | Cross-sectional | Single Item Necessity | 5       | 1.430  | 0.069 |
| Klinkman (2012)       | USA     | Depression         | 163  | 38%    | 35 (10)       | Prospective     | Brief Medication Questionnaire AND STAR'D Medication Adherence Questionnaire | 5       | 2.582  | 0.002 |
| Allen LaPointe et al. | USA     | Acute Coronary Syndrome groups | 972  | 6      | Medians for 6 groups | Prospective     | Self-report of no discontinuation nor missed doses in last reported 2) Beta-blocker and 3) Lipid-lowering therapy | 5       | 1.262  | 0.137 |
| Barnes et al. (2004)  | NZ      | Diabetes           | 82   | Not    | Reported 12.7; Tongan 5.92 (11.2) | Cross-sectional | MARS plus two items | 5       | 4.054  | 0.001 |
| Batchelder et al. (2013)| USA | Comorbid HIV and Type II Diabetes | 62   | 45%    | 52.8 (7.3)    | Cross-sectional | 5-item MARS 1) Antiretroviral 2) Diabetes | 5       | 1.300  | 0.306 |
| Beck et al. SWZ        | Schizophrenia | 150                | 65.3%| 44.9 (11.7) | Cross- Medication adherence | Necessity | 5       | 1.942  | 0.029 |
| Author and date | Country | Illness Group | N  | % male | Mean age (SD) | Study Design | Adherence measure                                                                 | BMQ (number of items) | OR  | p       |
|----------------|---------|---------------|----|--------|---------------|--------------|--------------------------------------------------------------------------------|----------------------|------|---------|
| Berglund et al. | SWE     | Statin Users  | 414| 50.8%  | 64.2 (9.5)   | Cross-sectional | subscale of the Service Engagement Scale (Tait et al., 2002)- clinician rated. Brief Adherence Rating Scale (BARS; Byerly et al., 2008) BARS selected for use here | Concerns (5)         | 2.266| <0.001 |
| Bhattacharya et al. | UK     | Colorectal or Breast Cancer | 43 | 44.2%  | 64.5 (7.4)   | Cross-sectional | Necessity (5) | Concerns (5)         | 1.338| 0.105 |
| Brown et al. | USA     | Depression    | 192| 29%    | 45.2 (16.0)  | Cross-sectional | Concerns (5) | Concerns (5)         | 0.570| 0.352 |
| Brown et al. (2013) | USA     | HIV           | 116| 58%    | 45.3 (8.6)   | Cross-sectional | VAS scale 0–100% used to rate adherence to each medication over the last month dichotomized at 95% | Necessity (8)         | 2.357| 0.014 |
| Butler et al. | UK      | Renal Transplant | 58 | 66%    | 48.0 (13)    | Cross-sectional | Electronic monitors\(c\) | Necessity (5)         | 4.871| 0.003 |
| Byer & Myers | UK      | Asthma        | 64 | 50%    | 39.6 (13.83) | Cross-sectional | Concerns (5) | Concerns (5)         | 0.517| 0.184 |
| Byrne et al. | IRE     | Coronary Heart Disease | 1084| 65% | 66.0 (9.1)   | Cross-sectional | 5-item MARS | Necessity (5)         | 2.551| <0.001 |
| Chisholm-Burns et al. | USA     | Renal Transplant | 512| 61.1%  | 52.4 (10.7)  | Cross-sectional | Immunosuppressant | Necessity (5)         | 2.065| <0.001 |
| Clatworthy et al. | UK     | Bipolar Disorders | 223| 36%    | 48 (11.2)    | Cross-sectional | 5-item MARS | Necessity (5)         | 2.114| 0.006 |
| Clifford et al. | UK      | Chronic illness | 146| 52%    | 64.3 (12.06) | Longitudinal Telephone call (*When Necessity (5) | 1.764| 0.090 |
| Author and date | Country | Illness Group | N     | % male | Mean age (SD) | Study Design | Adherence measure                                                                 | BMQ (number of items) | OR    | p      |
|----------------|---------|---------------|-------|--------|---------------|-------------|-----------------------------------------------------------------------------------|-----------------------|-------|--------|
| (2008) [142]   |         |               |       |        |               |             | was the last time you missed a dose of this medicine? Nonadherence defined as any dose missed in the previous 7 days b | Concerns (5)          | 0.457 | 0.020  |
| Cooper et al., UK HIV 234 84% 42 (8.9) Longitudinal At 48 weeks MASRI |          |               |       |        |               |             | (Walsh et al., 2002) scale-VAS % taken over last month dichotomized at 95% | Concerns (8)          | 0.499 | 0.004  |
| de Boer-van der NTL HIV 341 90% 45 Cross-sectional |          |               |       |        |               |             | Self report % of prescribed medicines taken | Concerns (11)         | 0.070 | 0.075  |
| Kolk et al. (2008) [183] |          |               |       |        |               |             | prescribed medicines taken | Concerns (8)          | 0.499 | 0.004  |
| De Las Cuevas ESP Affective 167 23.4% 56.1 (12.3) Longitudinal |          |               |       |        |               |             | 4-item MMAS | Concerns (5)          | 2.521 | 0.002  |
| De Smedt et al (2008) [184] | NTL Heart Failure 960 63.6% 69.6 (11.9) Cross-sectional |          |               |       |               |             | SECope non-adherence | Concerns (5)          | 0.484 | 0.112  |
| (2012) [185] |          |               |       |        |               |             | subsection (Johnson & Neilsands, 2007) | Concerns (5)          | 0.484 | 0.112  |
| de Thurah et al. DMK Rheumatoid 91 36% Median 63 Prospective |          |               |       |        |               |             | CQR 1) 9 months 2) | Concerns (5)          | 1.257 | 0.061  |
| (2010) [21] |          | Arthritis |       |        |               |             | baseline | Concerns (5)          | 0.420 | 0.132  |
| Ediger et al CAN IBD 326 40% 41.0 (14.06) Cross-sectional |          |               |       |        |               |             | 5-item MARS b | Concerns (5)          | 3.630 | 0.016  |
| (2007) [186] |          |               |       |        |               |             | Concerns (5) | 0.677 | 0.054  |
| Emilsson et al. SWE Asthma 35 28.6% 52.9 (14.7) Cross-sectional |          |               |       |        |               |             | Pill count | Concerns (5)          | 4.438 | 0.032  |
| (2011) [187] |          |               |       |        |               |             | Concerns (5) | 0.555 | 0.365  |
| Fawzi et al. EGT Adjustment Disorder with Depressed Mood 108 33.3% 61.3 (5.3) Cross-sectional |          |               |       |        |               |             | 10-item MARS | Concerns (5)          | 3.712 | 0.001  |
| (2012) [188] |          |               |       |        |               |             | Concerns (5) | 0.269 | 0.001  |
| Foo et al. SGP Glaucoma 344 64.8% 66.1 (10.2) Cross-sectional |          |               |       |        |               |             | 8-item MMAS dichot. at | Concerns (4)          | 1.045 | 0.837  |
| (2012) [189] |          |               |       |        |               |             | Concerns (5) | 2.778 | <0.0001 |
| French et al. UK Type II 453 57.4% 65.9 (10) Prospective |          |               |       |        |               |             | 5-item MARS 1) Baseline | Concerns (5)          | 1.295 | 0.232  |
| (2013) [23] |          | Diabetes |       |        |               |             | 2) Prospective | Concerns (5)          | 0.525 | 0.004  |
| (2012) [188] |          |               |       |        |               |             | Concerns (5) | 1.800 | 0.013  |
| Gauchet et al. FRA HIV 127 78% 39.7 (9.2) Cross-sectional |          |               |       |        |               |             | 16-item self-report | Concerns (5)          | 3.264 | 0.001  |
| (2007) [190] |          |               |       |        |               |             | Concerns (5) | 0.865 | 0.065  |
| Gatti et al. USA Chronic illness 275 27% - Cross-sectional |          |               |       |        |               |             | 8-item MMAS dichot. at | Concerns (5)          | 1.239 | 0.331  |
| Author and date | Country   | Illness Group | N   | % male | Mean age (SD) | Study Design | Adherence measure | BMQ (number of items) | OR    | p     |
|----------------|-----------|---------------|-----|--------|---------------|--------------|-------------------|----------------------|-------|-------|
| (2009) [191]   |           |               |     |        |               | sectional    | 1                 | Concerns (6)          | 0.357 | <0.001|
| George & CAN   | USA       | Heart Failure | 350 | 69%    | 61.0 (12.6)  | Cross-sectional | 1) Prescription dispensing | Necessity (5)                   | 1.529 | 0.069 |
| Shalansky      |           |               |     |        |               | sectional data (nonadherence) | defined as < 90% mean refill adherence | 0.954 | 0.539 |
| (2007) [192]   |           |               |     |        |               |              | 2) 4-item MMAS    |                      |       |       |
| Gonzalez et al. | USA   | HIV           | 325 | 60%    | 40.9 (8.5)   | Longitudinal randomised | 1) ACTG | Necessity (8)                  | 1.494 | 0.048 |
| (2007) [20]    |           |               |     |        |               |              | 2) MEMS cap – one drug | Concerns (11)         | 0.459 | <0.001|
| Griva et al.   | UK        | Kidney        | 218 | 59.6%  | 49.7 (12.3)  | Cross-sectional | 5-item MARS item plus | Necessity (5)                  | 7.278 | <0.001|
| (2012) [193]   |           |               |     |        |               |              | serum immunosuppressant concentrations | Concerns (5)                   |       |       |
| Grunfeldt et al | UK     | Breast Cancer | 110 | 0%     | 56.3 (7.0)   | Cross-sectional | 1) Asked “In the past” | Necessity (5)                  | 2.916 | 0.007 |
| (2005) [194]   |           |               |     |        |               |              | week have you taken your tamoxifen everyday? (Yes/No) | Concerns (11)         | 0.868 | 0.708 |
| Hedenrud et al. | SWE  | Migraine      | 174 | 16%    | Not calculable | Cross-sectional | 5-item MARS | Necessity (5)                  | 0.747 | 0.309 |
| (2008) [195]   |           |               |     |        |               |              | serum immunosuppressant concentrations | Concerns (5)                   | 0.588 | 0.064 |
| Horne et al.   | UK        | Cardiac and   | 210 | 49%    | 50.8 (16.2)  | Cross-sectional | 4-item RAM   | Necessity (5)                  | 2.018 | 0.006 |
| (1999) [14]    |           |               |     |        |               |              | serum immunosuppressant concentrations | Concerns (5)                   | 0.347 | <0.001|
| Horne & UK     | Asthma, Renal |               | 324 | 54%    | 54.1 (15.96) | Cross-sectional | 4-item MARS | Necessity (5)                  | 2.180 | <0.001|
| Weinman (1999) | [7]     | Cardiac, Oncology (pooled data) | | | | sectional | | Concerns (5)                   | 0.281 | <0.001|
| Horne et al.   | UK        | Renal         | 47  | 49%    | 49.0 (17.3)  | Cross-sectional | Single item: ‘How often’ | Necessity (5)                  | 1.115 | 0.842 |
| (2001) [196]   |           |               |     |        |               |              | do you deliberately miss a dose of medication? | Concerns (5)                   | 0.215 | 0.010 |
| Horne & UK     | Asthma    |               | 100 | 39%    | 49.3 (18.1)  | Cross-sectional | 9-item MARS | Necessity (6)                  | 3.405 | 0.002 |
| Weinman        |           |               |     |        |               |              | serum immunosuppressant concentrations | Concerns (11)         | 0.178 | <0.001|
| (2002) [168]   |           |               |     |        |               |              | serum immunosuppressant concentrations | Concerns (11)         | 0.524 | 0.095 |
| Horne et al.   | UK        | HIV           | 109 | 97%    | 41.2 (9.0)   | Cross-sectional | Single item: ‘How much’ | Necessity (8)                  | 1.773 | 0.126 |
| (2004) [197]   |           |               |     |        |               |              | of your HAART medication did you take within two hours of when you were supposed to? | Concerns (11)         | 0.524 | 0.095 |
| Horne et al.   | UK        | HIV           | 117 | 96%    | 37.8 (8.4)   | Prospective   | Single item: VAS from | Necessity (6)                  | 2.477 | 0.008 |
| Author and date | Country | Illness Group | N  | % male | Mean age (SD) | Study Design | Adherence measure | BMQ (number of items) | OR   | p     |
|----------------|---------|---------------|----|--------|--------------|--------------|------------------|----------------------|------|-------|
| (2007) [198]   |         |               |    |        |              |              |                  |                      |      |       |
| Horne et al.    | UK      | IBD           | 1871| 37%    | 50 (16.0)    | Cross-       | 4-item MARS     | Necessity (8)       | 1.790| <0.001|
| (2009) [167]   |         |               |    |        |              |              |                  |                      |      |       |
| Horne et al.    | UK      | Hypertension  | 230 | 88%    | 67.6         | sectional    |                  |                      |      |       |
| (2010) [24]    |         |               |    |        |              |              |                  |                      |      |       |
| (2010) [199]   |         | Affective Disorder | 35 | 28.6% | 45 (11)      | Cross-       | MMAS 4-item (dichot. at) | Necessity (5) | 0.881| 0.837 |
| Hou et al.      | UK      | Bipolar       | 35  | 28.6% | 45 (11)      | Cross-       | MMAS 4-item (dichot. at) | Necessity (5) | 0.680| 0.532 |
| Hunot et al.    | UK      | Depression    | 178 | 25%   | 40.1 (12.6)  | Longitudinal |                  |                      |      |       |
| (2007) [200]   |         |               |    |        |              |              |                  |                      |      |       |
| Iihara et al.   | JPN     | Hospital      | 151 | 62.3% | –            | Cross-       | Measure based on MMAS  | Necessity (5) | 1.998| 0.020 |
| (2010) [201]   |         |               |    |        |              |              |                  |                      |      |       |
| Johnson et al.  | USA     | HIV           | 295 | 100%  | 45.2 (10.1)  | Cross-       | 1) ACTG 3 days (%) | Necessity (5) | 0.960| 0.365 |
| (2012) [29]    |         |               |    |        |              |              |                  |                      |      |       |
| Johnsdottir et al.| UK    | Schizophrenia/ | 280 | 51%   | 35.1         | Cross-       | VAS (0%–100%)    | Necessity (8) | 5.887| <0.001|
| Kemp et al.     | UK      | Epilepsy      | 37  | 51%   | 40.7 (SD not reported) | Cross- | Low-dose of phenobarbital indicative of nonadherence, and/or measurement of antiepileptic drug levels | Necessity (5) | 0.493| 0.057 |
| (2007) [203]   |         |               |    |        |              |              |                  |                      |      |       |
| Khandheria et al.| USA    | Coronary Artery| 132 | 83%   | 65.8 (10.1)  | Cross-       | 4-item MMAS     | Necessity (5) | 1.050| 0.875 |
| (2008) [204]   |         |               |    |        |              |              |                  |                      |      |       |
| Kressin et al.  | USA     | Hypertension  | 806 | 35%   | 59           | Cross-       | Hill-Bone Compliance to | Necessity (5) | 1.414| 0.200 |
| (2010) [205]   |         |               |    |        |              |              |                  |                      |      |       |
| Kronish et al.  | USA     | Stroke or TIA | 600 | 60.6% | 63.4 (11.2)  | Cross-       | 8-item MMAS dichot. at | Necessity (5) | 1.120| 0.557 |

BMQ (number of items): it is not specified for all studies.

OR: odds ratio.

p: p-value.
| Author and date | Country | Illness Group     | N     | % male | Mean age (SD) | Study Design | Adherence measure                                                                 | BMQ (number of items) | OR    | p     |
|----------------|---------|-------------------|-------|--------|---------------|-------------|------------------------------------------------------------------------------------|-----------------------|-------|-------|
| (2013) [206]  | NZ      | Heart, Liver,     | 326   | 64.4%  | Heart         | Cross-      | Concerns (4) modified [193]                                                          |                      |       |       |
|                |         | Lung Transplant   |       |        | section       |             | Imunosuppressant                                                                   |                      |       |       |
| Kung et al.    |         |                   |       |        |               |             | Therapy Adherence Scale (ITAS) <12 non-adherence                                    |                      |       |       |
| (2012) [207]  | NZ      | Heart, Liver,     | 326   | 64.4%  | Heart         | Cross-      | Concerns (5)                                                                       |                      |       |       |
|                |         | Lung Transplant   |       |        | section       |             | Necessity (5)                                                                       |                      |       |       |
| Llewellyn et al. [208] | UK | Haemophilia      | 65    | 100%   | 36.4 (12.2)   | Cross-      | 1) Adherence to frequency of prophylactic Concerns (5)                              |                      |       |       |
| et al. (2003) [22] |       |                   |       |        |               |             | Necessity (5)                                                                       |                      |       |       |
|                |         |                   |       |        |               |             | infusion with clotting Necessity (5)                                                |                      |       |       |
|                |         |                   |       |        |               |             | Therapy adherence scale (ITAS) <12 non-adherence                                     |                      |       |       |
| Maguire et al. [208] | UK | Hypertension     | 327   | 46%    | Not reported  | Cross-      | Concerns (5)                                                                       |                      |       |       |
| (2008) [208]  |         |                   |       |        |               |             | Necessity (5)                                                                       |                      |       |       |
| Mahler et al.  | GMY     | Mixed Chronic     | 360   | 53.3%  | 69.5 range 19-| Cross-      | Concerns (5)                                                                       |                      |       |       |
| (2012) [209]  |         |                   |       |        | section       |             | Necessity (5)                                                                       |                      |       |       |
| Maidment et al. [209] | UK | Depression      | 67    | 49%    | 74.2 (6.1)    | Cross-      | Concerns (5)                                                                       |                      |       |       |
| et al. (2002) [15] |       |                   |       |        |               |             | Necessity (5)                                                                       |                      |       |       |
| Menckeberg et al. [210] | NTL | Asthma          | 238   | 33%    | 36.2 (6.3)    | Cross-      | Concerns (5)                                                                       |                      |       |       |
| al. (2008)     |         |                   |       |        |               |             | Necessity (5)                                                                       |                      |       |       |
| Moshkovska et al. [210] | UK | Ulcerative  | 169   | 51%    | 49 (SD not | Cross-      | Concerns (5)                                                                       |                      |       |       |
| al. (2009)     |         |                   |       |        | reported      |             | Necessity (5)                                                                       |                      |       |       |
| Nikolitina et al. [210] | USA | Epilepsy        | 72    | 37.5%  | 44 (14.2)     | Cross-      | Concerns (5)                                                                       |                      |       |       |
| (2011) [212]  |         |                   |       |        | section       |             | Necessity (5)                                                                       |                      |       |       |
| Neame & Hammond (2005) [213] | UK | Rheumatoid  | 344   | 33%    | 49.5% aged   | Cross-      | Concerns (5)                                                                       |                      |       |       |
| Nicklas et al. [214] | UK | Chronic Pain | 217   | –      | –             | Cross-      | Concerns (5)                                                                       |                      |       |       |
| O’Carroll et al. [215] | UK | Liver          | 33    | 52%    | 55.8 (13.37)  | Cross-      | Concerns (5)                                                                       |                      |       |       |
| (2006) [215]  |         |                   |       |        | section       |             | Concerns (5)                                                                       |                      |       |       |

Table 1. Cont.
| Author and date   | Country | Illness Group | N    | % male | Mean age (SD) | Study Design | Adherence measure       | BMQ (number of items) | OR   | p     |
|------------------|---------|---------------|------|--------|---------------|--------------|------------------------|----------------------|------|-------|
| O’Carroll et al. | UK      | Ischaemic     | 180  | 54%    | 69 (11.4)     | Cross-sectional | salicylic acid/creatinine | 1) Baseline           | Necessity (5)        | 0.705 | 0.202 |
|                  |         | Stroke        |      |        |               |              |                        | 2) Prospective        | Necessity (5)        | 0.209 | <0.001|
| Ovchinikova et   | AUS     | Asthma        | 134  | 31%    | 53 (19)       | Longitudinal  | MARS 1) Baseline 2)    | Necessity (5)         | 1.249 | 0.262 |
| al. (2011) [26]  |         |               |      |        |               |              |                        | Prospective           | Necessity (5)        | 0.220 | <0.001|
| Percival et      | AUS     | Heart Failure | 43   | 83.7%  | 64.2 (17.1)   | Cross-sectional | 5-item MARS dichot. at | Necessity (5)        | 3.068 | 0.165 |
| al. (2012) [216] |         |               |      |        |               |              |                        | Concerns (5)          | 0.508 | 0.399 |
| Peters et al.    | USA     | Marfan        | 174  | 42%    | 39.8 (12.2)   | Cross-sectional | 3-item self-report measure | Necessity (5)        | 1.299 | 0.417 |
| (2001) [217]     |         | Syndrome      |      |        |               |              |                        | (adapted from MARS)   | Necessity (5)        | 0.424 | 0.010 |
| Phatak & Thomas  | USA     | Hypertension, 250 | 38% | <30 (11.2%) | Cross- sectional | 9-item MMAS | Necessity (5)        | 1.550 | 0.059 |
|                  |         | Arthritis, Back |     | 30–39 (14%) |                     |              |                        | Concerns (6)          | 0.215 | <0.001|
|                  |         | Asthma, Hypercholesterolemia | | 50–59 (24.4%) |               |              |                        |                      |                  |       |
| Rajpura & Nayak  | USA     | Hypertension 117 | 64.1% | 55–65 (23.9%) | Cross- sectional | MMAS | Necessity (5)        | 2.551 | 0.008 |
| (2013)           |         | and aged 55 or over |       | >65 (52.1%) |               |              |                        | Concerns (5)          | 0.423 | 0.014 |
| Rees et al.      | AUS     | Glaucoma      | 131  | 61.1%  | 67.7 (13.6)   | Cross- sectional | 4-item RAM | Necessity (5)        | 1.966 | 0.035 |
| (2010)           |         |               |      |        |               |              |                        | Concerns (8)          | 0.651 | 0.180 |
| Rees et al.      | USA, SGP, AUS | Glaucoma 475 | 55.4% | African | Cross- sectional | 4-item RAM | Necessity (5)        | 2.385 | <0.001|
| (2013) [220]     |         |               |      |        |               |              |                        |                      | 0.414 | <0.001|
| Reynolds et al.  | USA     | Osteoporosis 193 | 0%  | | Cross- sectional | Osteoporosis Specific 8-item MMAS | Necessity (5) | 3.405 | <0.001|
| (2012)           |         |               |      |        |               |              |                        | Concerns (6)          | 0.424 | 0.005 |
| Ross et al.      | UK      | Hypertension 515 | 52% | 59.9 (12.16) | Cross- sectional | 4-item MMAS | Necessity (5)        | 3.060 | 0.001 |
| (2004) [159]     |         |               |      |        |               |              |                        | Concerns (5)          | 0.501 | 0.306 |
| Ruppert et al.   | Hypertension 33 | 21% | 70.6 (9.1) | Prospective | MEMS for 6 weeks post- | Necessity (5) | 0.51 | 0.053 |
| (2012) [222]     |         |               |      |        |               |              |                        | BMQ                  | Necessity (5)        | 1.115 | 0.786 |
| Author and date | Country | Illness Group | N     | % male | Mean age (SD) | Study Design | Adherence measure | BMQ (number of items) | OR  | p    |
|----------------|---------|---------------|-------|--------|---------------|--------------|-------------------|-----------------------|-----|------|
| Kazantzis (2008) [223] | USA     | Type II       | 608   | 48%    | 62.1 (9.2)   | sectional    | Concerns (14)     |                       | 0.269 | 0.002 |
| Schoenthaler et al. (2012) [224] | Diabetes | MPR over last 2 years | 608   | 48%    | 62.1 (9.2)   | Cross-       | Necessity (5)      |                       | 0.757 | 0.060 |
| Schuz et al. (2011) [225] | GMY Older Adults with Comorbid Illnesses | 309   | 59.3% | 73.3 (5.1) | Longitudinal | 2 items from RAM | Necessity (2)       | 1.353 | 0.155 |
| Nelson (2011) [226] | USA Diabetes | sectional | 16    | 0%     | 46.1 (10.2)  | Cross-       | 4-item MMAS        |                       | 0.917 | 0.931 |
| Sirey et al. (2013) [227] | USA Older Adults with Comorbid Illnesses | 299   | 22.1% | 75.6 (7.3); Adherent 76.7 (7.4) | sectional | Concerns (2) |                       | 0.494 | 0.001 |
| Sofianou et al. (2012) [228] | USA Asthma | sectional | 242   | 16.1%  | 67.4 (6.8)   | Cross-       | 10-item MARS       |                       | 2.353 | <0.001 |
| Tibaldi et al. (2009) [229] | Italy Chronic Illness | sectional | 427   | 45%    | 59 (14)      | Cross-       | 5-item MARS        |                       | 1.314 | 0.123 |
| Sud et al. (2005) [60] | USA Acute Coronary Syndrome | sectional | 208   | 60.6% | 64.9 (13.0)  | Cross-       | 4-item MARS        |                       | 1.800 | 0.022 |
| Trachtenberg et al. (2004) [230] | UK Rheumatoid | sectional | 371   | 47.4%  | 24.0 (12.6)  | Longitudinal | Self-reported number of Mason     |                       | 0.694 | 0.256 |
| Unni & Farris (2011a) [33] | USA Cholesterol | Lowring | 85    | 25%    | 58.9 (12.64) | Cross-      | 1) 19-item CQR   | Necessity (5)       | 3.758 | <0.001 |
| Unni & Farris (2011b) [27] | USA Older Adults | Medication Maintenance Patients | 1061  | 45.6%  | 73.2 (9.2)   | Cross-       | 4-item MMAS 1) time 1; 2) time 2 | Necessity (5) | 1.010 | 0.931 |
| Uusku¨ la et al. (2011a) [33] | EST HIV | sectional | 161   | 55%    | 72.5 (5.5)   | Recall of proportion of |                       | 0.503 | <0.001 |

**BMQ:** Brief Medicine Questionnaire; **MPR:** Medication Possession Ratio; **MMAS:** Morisky Medication Adherence Scale; **MARS:** Medical Adherence Rating Scale; **CQR:** Credibility and Qualitative Rating Scale; **DFO:** Direct Falcon’s Osteitis; **HIV:** Human Immunodeficiency Virus.
| Author and date | Country | Illness Group | N | % male | Mean age (SD) | Study Design | Adherence measure | BMQ (number of items) | OR | p |
|----------------|---------|---------------|---|--------|--------------|-------------|------------------|----------------------|----|----|
| (2012) [231]   | NTL     | Rheumatoid    | 228 | 33%    | 56.2 (12.2)  | Cross-sectional | Self-report | Concerns (7) | 0.250 | 0.073 |
| et al. (2009) [232,233] | Arthritis | sectional | | | | | | | |
| Voils et al. (2012) [233] | USA | Hypertension | 201 | 86% | 64.1 (11.0) | Cross-sectional | 8-item MMAS | Necessity (5) | 1.516 | 0.442 |
| (2012) [234] | sectional | | | | | | | |
| Wileman et al. (2011) [234] | UK | End-Stage | 76 | 60.5% | 63.1 (15.4) | Cross-sectional | Medications adherence | Necessity (5) | 1.641 | 0.270 |
| (2011) [234] | sectional | | | | | | | |
| Wong & Mulherin (2007) [235] | UK | Rheumatoid | 68 | 40% | 55.8 (13.0) | Longitudinal | Patient report of drug | Necessity (5) | 1.319 | 0.568 |
| Yu et al. (2012) [236] | SGP | Peritoneal | 20 | 60% | 64.4 (11.6) | Cross-sectional | Specially designed 5 item | Necessity (5) | 1.828 | 0.499 |
| (2012) [237] | Dialysis | sectional | | | | | | | |
| Zerah et al. (2012) [237] | FRA | Patients taking glucocorticoids | 182 | 21% | Median 47 | Cross-sectional | 4-item MMAS | Necessity (5) | 2.008 | 0.042 |
| Note. NZ = New Zealand; IRE = Ireland; NTL = Netherlands; CAN = Canada; FRA = France; SWE = Sweden; IRI = Iran; SWZ = Switzerland; ESP = Spain; DMK = Denmark; EGT = Egypt; SGP = Singapore; JPN = Japan; EST = Estonia; GMY = Germany; AUS = Australia; IBD = inflammatory bowel disorder; TIA = Transient Ischemic Attack; MARS is the Medication Adherence Rating Scale from Thompson, Kulkarni, & Sergejew (2000); MEMS is Medication Event Monitoring System; CQ-R is the Compliance Questionnaire-Rheumatology from de Klerk, van der Heijde, Landewe, van der Tempel, & van der Linden (2003); MMAS is the Morisky Medication Adherence Scale from Morisky, Green, & Levine (1986); TxEQ is the Transplant Effects Questionnaire from Ziegelmann et al. (2002); ACTG is the Adherence to Combination Therapy Guide from Chesney et al., 2000; RAM is the Reported Adherence to Medication Scale from Horne et al., (1999), renamed MARS (Medication Adherence Report Scale); VAS = visual analogue scale. |
| Adherence result selected for use in meta-analysis; |
| Relationship between adherence measure and BMQ scales not reported. |
| doi:10.1371/journal.pone.0080633.t001 |
Necessity and Concerns items included (since items may be added specific to the medication prescribed), the adherence measure used, information (means and standard deviations, odds ratios and 95% confidence intervals or correlation coefficients) to calculate the effect size between adherence and Necessity beliefs and Concerns, and the p-value. Where the full required statistics were not reported, authors were contacted for further information.

Methodology/Quality Assessment

A simple methodology assessment tool was devised for this study. Methodology was assessed by two of three independent expert raters (SC, RP and VC) using the following parameters:

- study location (UK or non-UK)
- study design (cross-sectional or longitudinal/prospective)
- measure of adherence (self-report or objective measure [electronic monitors, prescription redemption, blood test results])

- sample size ($<82 = 0$ or $\geq 82 = 1$). This was based on the sample needed to detect a medium effect size for a correlation ($r = 0.3$) with an alpha level of 0.05 and 80% power.

Ratings were completed independently and then combined. There were no disagreements regarding ratings.

Statistical Analysis

The primary outcome measure was adherence to medication. For each study, the effect size was expressed as an odds ratio with 95% confidence intervals. Where studies reported the standard mean difference or correlation coefficient, the effect size was converted into an odds ratio, using the Comprehensive Meta-Analysis program. We used a random effects model to accommodate heterogeneity between studies which was anticipated due to differences with respect to sample characteristics, study design and the adherence measure used.

The presence of significant heterogeneity across studies was examined using the chi-squared statistic ($Q$). The magnitude of this heterogeneity across studies was estimated using the $I^2$ statistic.
Sample Characteristics

The mean age of participants in the 94 included studies ranged from 24.0 to 74.2, with an overall mean age of 55.8 (it was not possible to calculate the mean age in 13 studies). The percentage of males ranged from 0–100% (breast cancer and haemophilia samples respectively), with an overall percentage of males of 49.7% male (excluding 3 studies where it was not possible to calculate the number of males). Sample sizes ranged from 16 to 1071.

The total sample, N= 25,072, encompassed patients with asthma, renal disease, organ transplantation, dialysis chronic pain, kidney transplantation, cancer, cardiovascular disorders, Marfan’s syndrome, depression, haemophilia, diabetes, HIV, rheumatoid arthritis, osteoporosis, thalassemia, inflammatory bowel disease, bipolar disorder, schizophrenia, epilepsy, migraine, back problems, glaucoma and mixed chronic illness.

Thirty-three studies (35.1%) used the MARS to measure adherence, 20 used the Morisky Medication Adherence Scale (21.2%), 3 used pharmacy refill (3.2%), 3 used electronic monitoring (3.2%) and two or fewer studies used the remaining measures.

Effect Sizes

Necessity beliefs. There was a significant relationship between Necessity beliefs and adherence, OR=1.742, 95% CI [1.569, 1.934], p<0.0001. There was significant heterogeneity between the 96 comparisons from 94 studies, Q(95) = 422.662, p<0.001, which was substantial in magnitude, I² = 77.52%.

Figure 2 presents the individual effect-size estimates and shows that the relationship between Necessity beliefs and adherence was significant (p<0.05) for 49 (51.0%) of the included studies. Sensitivity analyses revealed that the overall result was not affected when any single finding was omitted.

Concerns. There was a significant relationship between Concerns and adherence and fewer Concerns about adverse effects, OR = 0.502, 95% CI [0.450, 0.560], p<0.0001. There was significant heterogeneity among the 93 comparisons from 91 studies, Q(92) = 481.84, p<0.001, suggesting that factors other than chance accounted for a moderate-substantial amount of variance, I² = 80.91%.

Figure 3 presents the individual effect-size estimates and shows that the relationship between concerns and adherence was significant (p<0.05) for 53 (57.0%) of the included studies. Sensitivity analyses revealed that the overall result did not change when any single finding was omitted.

Stratification by Long-Term Condition and Measurement

See Tables 2 and 3 for OR stratified by different long-term conditions and adherence measures. Two few studies reported data on the majority of conditions and measures to allow statistical tests for heterogeneity.

Methodology/Quality Assessment

See Table 4 for sensitivity analyses.

Study location. Most studies were conducted outside of the UK (n=62; 66.0%). Stronger effects were apparent for both Necessity and Concerns for studies conducted in the UK relative to studies conducted outside of the UK, however the relationship between Necessity and Concerns was significant for both locations. Substantial and significant heterogeneity was present in all analyses.

Study design. The majority of studies (n = 77, 81.9%) were cross-sectional, with few studies using longitudinal or prospective designs (n = 17; 18.1%). Effect sizes were similar for longitudinal/prospective and cross-sectional designs for both Necessity and Concerns. Substantial and significant heterogeneity was present in all analyses.

Measurement of adherence. Eighty-three studies (88.3%) employed measured adherence using self-report, while 11 (11.7%) used other methods. The association between adherence and
Figure 2. Forest plot of effect sizes for BMQ Necessity and medication adherence. doi:10.1371/journal.pone.0080633.g002
Figure 3. Forest plot of effect sizes for BMQ Concerns and medication adherence.

doi:10.1371/journal.pone.0080633.g003
Table 2. Analyses Stratified By Long-Term Condition.

| Condition                                      | $k$ | OR   | (95% CI)     | $p$   |
|------------------------------------------------|-----|------|--------------|-------|
| Necessity                                      |     |      |              |       |
| Asthma                                         | 7   | 2.610| 1.802–3.780  | <0.001|
| Bipolar disorder                               | 2   | 1.624| 0.739–3.567  | 0.227 |
| Blood disorders                                | 3   | 1.512| 0.580–3.944  | 0.398 |
| Cancer                                         | 2   | 2.313| 1.190–4.496  | 0.013 |
| Depression                                     | 8   | 1.989| 1.382–2.862  | <0.001|
| Diabetes                                       | 6   | 1.502| 0.930–2.425  | 0.096 |
| Dialysis/end stage renal disease               | 3   | 1.454| 0.771–2.742  | 0.247 |
| Epilepsy                                       | 2   | 0.859| 0.284–2.602  | 0.789 |
| Glaucoma                                       | 3   | 1.697| 0.976–2.949  | 0.061 |
| High cholesterol                               | 2   | 1.497| 0.659–3.401  | 0.335 |
| HIV                                            | 9   | 1.742| 1.242–2.444  | 0.001 |
| Hypertension                                   | 7   | 1.426| 0.980–2.075  | 0.064 |
| IBD                                            | 3   | 1.775| 1.560–2.020  | <0.001|
| Mixed sample                                   | 11  | 1.504| 1.249–1.810  | <0.001|
| Organ transplant                               | 5   | 2.875| 1.561–5.294  | 0.001 |
| Pain                                           | 2   | 1.239| 0.468–3.280  | 0.666 |
| Rheumatoid arthritis                           | 5   | 3.277| 1.106–9.708  | 0.032 |
| Schizophrenia                                  | 2   | 3.301| 1.115–9.777  | 0.031 |
| Stroke/CHD/acute coronary syndrome              | 9   | 1.402| 1.022–1.924  | 0.036 |

Concerns

| Condition                                      | $k$ | OR   | (95% CI)     | $p$   |
|------------------------------------------------|-----|------|--------------|-------|
| Asthma                                         | 6   | 0.406| 0.304–0.541  | <0.001|
| Bipolar disorder                               | 2   | 0.410| 0.250–0.672  | <0.001|
| Blood disorders                                | 3   | 0.764| 0.545–1.073  | 0.121 |
| Cancer                                         | 2   | 0.771| 0.411–1.445  | 0.417 |
| Depression                                     | 8   | 0.408| 0.215–0.772  | 0.006 |
| Diabetes                                       | 6   | 0.450| 0.202–1.003  | 0.051 |
| Dialysis/end stage renal disease               | 3   | 0.509| 0.211–1.232  | 0.134 |
| Epilepsy                                       | 2   | 0.662| 0.327–1.339  | 0.251 |
| Glaucoma                                       | 3   | 0.909| 0.258–3.204  | 0.882 |
| High cholesterol                               | 2   | 0.598| 0.123–2.918  | 0.525 |
| HIV                                            | 9   | 0.619| 0.465–0.824  | 0.001 |
| Hypertension                                   | 6   | 0.433| 0.340–0.552  | <0.001|
| IBD                                            | 3   | 0.612| 0.536–0.698  | <0.001|
| Mixed sample                                   | 11  | 0.423| 0.339–0.501  | <0.001|
| Organ transplant                               | 4   | 0.486| 0.356–0.503  | <0.001|
| Pain                                           | 2   | 0.620| 0.428–0.897  | 0.011 |
| Rheumatoid arthritis                           | 5   | 0.608| 0.385–0.962  | 0.033 |
| Schizophrenia                                  | 2   | 0.648| 0.410–1.025  | 0.063 |
| Stroke/CHD/acute coronary syndrome              | 9   | 0.518| 0.382–0.704  | <0.001|

Note. CHD = coronary heart disease. doi:10.1371/journal.pone.0080633.t002

Table 3. Analyses Stratified by Adherence Measure.

| Measure                                        | $k$ | OR   | (95% CI)     | $p$   |
|------------------------------------------------|-----|------|--------------|-------|
| Necessity                                      |     |      |              |       |
| Brief Medication Questionnaire                  | 2   | 2.350| 1.122–4.341  | 0.022 |
| CQ-R                                           | 2   | 18.327| 5.696–58.967 | <0.001|
| Electronic monitoring                          | 3   | 1.625| 0.599–4.412  | 0.340 |
| MARS                                           | 33  | 1.838| 1.581–2.137  | <0.001|
| MASRI                                          | 2   | 2.048| 1.390–3.018  | <0.001|
| MMAS                                           | 20  | 1.558| 1.305–1.862  | <0.001|
| Pharmacy refill                                | 3   | 1.668| 0.684–4.066  | 0.260 |

Concerns

| Measure                                        | $k$ | OR   | (95% CI)     | $p$   |
|------------------------------------------------|-----|------|--------------|-------|
| Brief Medication Questionnaire                  | 2   | 0.415| 0.131–1.321  | 0.137 |
| CQ-R                                           | 2   | 0.546| 0.286–1.044  | 0.067 |
| Electronic monitoring                          | 3   | 0.620| 0.403–0.946  | 0.027 |
| MARS                                           | 31  | 0.425| 0.362–0.500  | <0.001|
| MASRI                                          | 2   | 0.410| 0.251–0.669  | <0.001|
| MMAS                                           | 20  | 0.590| 0.426–0.817  | 0.002 |
| Pharmacy refill                                | 3   | 0.785| 0.630–0.979  | 0.031 |

Note. CQ-R = Compliance Questionnaire- Rheumatology from de Klerk, van der Heijde, Landewé, van der Tempel, & van der Linden (2003), MARS = Medication Adherence Report Scale Scale from Horne et al., (1999), MASRI = Medication Self-Report Index from Walsh et al., 2002, MMAS = Morisky Medication Adherence Scale from Morisky, Green, & Levine (1986). doi:10.1371/journal.pone.0080633.t003

Statistical power. Eighteen (19.1%) of the studies were classed as having small samples (less than 82). The size of the associations between Necessity and Concerns and adherence were similar for smaller and larger studies. Heterogeneity estimates indicated that variability around the larger samples estimates was substantial. However, the smaller sample estimates were less heterogeneous, with $I^2$ values in the small range for Concerns and the moderate range for Necessity beliefs.

Assessment of Risk of Publication Bias

Necessity. The fail-safe $N (Nfs)$ was 96, indicating that there would need to be $\geq 96$ unpublished findings of an equal magnitude but opposite direction, to reverse our conclusion that a significant effect exists. Inspection of the funnel plot suggested asymmetry (see Figure 4), however Duval and Tweedie’s trim and fill method did not suggest that studies should be added/removed. Egger’s t-test was significant, $t(94) = 1.60$, $p<0.001$, suggesting the presence of asymmetry.

Concerns. The fail-safe $N (Nfs)$ was 94, indicating that there would need to be $\geq 94$ unpublished findings of an equal magnitude but opposite direction, to reverse our conclusion that a significant effect exists. Funnel plot inspection suggested the presence of asymmetry (see Figure 5), which was confirmed by a significant Egger’s t-test, $t(91) = 1.80$, $p<0.001$. Further, Duval and Tweedie’s trim and fill method suggested 13 studies should be added/removed to make the funnel plot symmetrical. The location of the imputed studies indicated that the asymmetry may arise from a lack of reporting of studies which find a negative relationship between concerns and adherence. However, the similarity between the adjusted OR 0.567 95% CI [0.507, 0.634], which includes the imputed trimmed and filled studies, and the observed OR 0.504 95% CI [0.450, 0.564], suggests that any bias does not have a large impact on the findings.
This meta-analytic review indicates that the Necessity-Concerns Framework (NCF) is a potentially useful model for understanding patients’ evaluations of prescribed medicines. The magnitude of the aggregate effect sizes indicates that, for each standard deviation increase in Necessity beliefs, the odds of adherence increases by a factor of 1.7. Conversely, for each standard deviation increase in Concerns, the odds of adherence decreases by a factor of 2.0.

Strengths and Limitations of the Study

The sensitivity and publication bias analyses conducted confirm our hypothesis that Necessity beliefs and Concerns are associated with adherence/nonadherence to medicines, across a wide range of conditions, medications, and study locations. No research synthesis can transcend the limitations of the primary studies. However, sensitivity analyses confirmed that this association is robust across methodological features; remaining when small, underpowered studies were removed, when only longitudinal/prospective designs were included, and when self-report and non self-report adherence assessments were included separately. The majority of the studies relied solely on self-reported adherence. Self-report measures have high face validity and high specificity for nonadherence, however they may be subject to self-presentation and recall bias [161]. Thus some people may be reporting higher adherence rates than they actually attain. This bias does not diminish our confidence in the finding that beliefs were related to adherence, as there is no evidence that such a bias would be associated with medication beliefs. Indeed some patients with high Concerns and low Necessity beliefs may be expected to incorrectly report high adherence in order to present themselves positively. This pattern would attenuate the relationship found between adherence and medication beliefs, making it less likely that we would find an association between beliefs and adherence. Moreover, given that this relationship remained when non-self report measures were used, we are confident that the observed relationships between beliefs and adherence are not an artifact arising from the limitations of self-report. Only published studies were included, creating a possible bias, since studies submitted for publication may be more likely to have positive results and larger effect sizes. Since for both Necessity beliefs and Concerns, the fail safe N indicated that the number of additional negative findings required to accept our null hypothesis was similar to the number of studies included in this meta-analysis, and there was little suggestion of publication bias through funnel plot analysis, our findings appear to reflect a true relationship between beliefs and adherence.

Table 4. Analyses Stratified By Adherence Measure, Study Location, Design and Power.

|                      | k     | OR   | (95% CI) | \(p\)  | \(I^2\)  | Heterogeneity test |
|----------------------|-------|------|----------|--------|---------|-------------------|
| **Necessity**        |       |      |          |        |         |                   |
| UK study             | 32    | 2.201| 1.786-2.713| <0.001 | 72.72%***| \(Q(1) = 7.67, \ p<0.05\) |
| Non-UK study         | 64    | 1.573| 1.405-1.761| <0.001 | 74.79%***|                   |
| **Concerns**         |       |      |          |        |         |                   |
| UK study             | 31    | 0.403| 0.335-0.485| <0.001 | 62.75%***| \(Q(1) = 7.61, \ p<0.05\) |
| Non-UK study         | 62    | 0.555| 0.486-0.635| <0.001 | 82.48%***|                   |
| **Subjective adherence measure** | 83    | 1.737| 1.565-1.929| <0.001 | 75.54%***| \(Q(1) = 0.031, \ p=0.86\) |
| **Objective adherence measure** | 13    | 1.817| 1.114-2.963| 0.017  | 86.20%***|                   |
| **Concerns**         |       |      |          |        |         |                   |
| Subjective adherence measure | 81    | 0.485| 0.429-0.549| <0.001 | 82.84%***| \(Q(1) = 13.55, \ p<0.001\) |
| Objective adherence measure | 12    | 0.726| 0.609-0.866| <0.001 | 8.93%    |                   |
| **Prospective/longitudinal** | 18    | 1.526| 1.243-1.874| <0.001 | 63.02%***| \(Q(1) = 1.82, \ p=0.18\) |
| **Cross-sectional**  | 78    | 1.798| 1.595-2.027| <0.001 | 79.49%***|                   |
| **Concerns**         |       |      |          |        |         |                   |
| Prospective/longitudinal | 18    | 0.449| 0.356-0.567| <0.001 | 70.88%***| \(Q(1) = 1.14, \ p=0.29\) |
| Cross-sectional      | 75    | 0.519| 0.458-0.588| <0.001 | 81.28%***|                   |
| **Necessity**        |       |      |          |        |         |                   |
| Low power            | 18    | 1.848| 1.290-2.646| 0.001  | 46.19%*  | \(Q(1) = 0.12, \ p=0.73\) |
| High power           | 78    | 1.730| 1.550-1.930| <0.001 | 80.16%***|                   |
| **Concerns**         |       |      |          |        |         |                   |
| Low power            | 17    | 0.488| 0.371-0.643| <0.001 | 0.00%    | \(Q(1) = 0.05, \ p=0.82\) |
| High power           | 76    | 0.505| 0.448-0.570| <0.001 | 83.83%***|                   |

Note. *\(p<.05\), **\(p<.001\) for Q statistic.

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injections, or if practical barriers to care may be of relatively greater importance in some groups using medications administered through different routes.

Eighteen studies assessed whether Concerns and Necessity beliefs could predict adherence using longitudinal/prospective designs. The relationship was not reduced in these studies, supporting the proposal that medication beliefs can influence adherence.

Figure 4. Funnel plot for BMQ Necessity and medication adherence.
[Link: doi:10.1371/journal.pone.0080633.g004]

Figure 5. Funnel plot for BMQ Concerns and medication adherence.
[Link: doi:10.1371/journal.pone.0080633.g005]
later adherence as part of the self-regulation of illness [14]. We did not restrict our inclusion criteria to studies published in English. However, our search only identified one study published in any other language, despite the fact that the BMQ was translated into the native language for the study. Cultural values [162] can impact on the way in which individuals interact with the healthcare system. However, variations in treatment necessity and concerns and association between these beliefs and adherence were noted across different countries, languages and cultures. We found that studies outside the UK, where the BMQ and its disease-specific modifications have been predominantly developed, found reduced associations between necessity and concerns beliefs and adherence. Further work is needed to investigate potential cultural variations in medication beliefs.

Implications for Research and Practice

The development of more effective methods for addressing nonadherence is a priority for research and practice [1,5]. Our findings suggest, that novel interventions to support informed choice and optimal adherence to appropriately prescribed medicines are likely to be more effective if they take account of patients’ beliefs about the treatment and how they judge their personal need for the prescription relative to concerns about potential adverse consequences of taking it. Necessity beliefs and Concerns may trigger intentional nonadherence, for example, if patients decide not to take their medication due to concerns regarding potential or actual adverse consequences, and unintentional nonadherence, (e.g. if patients who believe a medicine is not important for their health forget to take it). Beliefs can have counter-balancing effects on adherence, such as when patients continue to take a medication they believe is essential for their health despite concerns regarding adverse effects. The challenge now is to develop effective interventions to address patients’ doubts about the necessity for treatment and concerns about adverse consequences in order to enhance adherence. The challenge goes beyond ‘getting patients to take more medicines’. Our findings show that many patients harbour significant, unresolved doubts and concerns about prescribed treatment suggesting a fault-line between patients’ and prescribers’ cultural perceptions of the treatment. Viewed from the perspective of biomedicine, nonadherence may seem irrational. However, from the patients’ perspective, nonadherence may be a ‘common-sense’ response to their implicit appraisal of the treatment. For some patients nonadherence might represent an informed choice. In this case the outcome of ‘adherence support’ would be to avoid prescribing an unwanted treatment, to the relief of patient and payer. However, for others, evaluations of treatment necessity and concerns may be based on misconceptions about the illness and treatment.

More detailed studies of patient representations illness and treatment show that, even when treatment evaluations are based on misconceptions they appear to draw on a ‘common-sense’ logic [12,163,164]. For example, the need for daily medication may seem less salient when symptoms are absent or cyclical [165–167]. Concerns about prescribed medication are not just related to side effects but are common, even when the medication is well tolerated. They are often related to beliefs about the negative effects of medication and include worries about long-term effects, dependence, cost of medication and dislike of having to rely on medicines [14,167]. Concerns are related to more general beliefs about pharmaceuticals as a class of treatment which are often perceived as intrinsically harmful and over-prescribed by doctors [167,168]. The package information leaflets, dispensed with many prescription medicines may exacerbate concerns as they list all possible side effects, leaving patients with outstanding questions and making it difficult to understand the likely risk and place them in context with potential benefits [169].

Nonadherence is often a hidden problem. Patients may be reluctant to express doubts or concerns about prescribed medication and to report nonadherence; sometimes because they fear that this will be perceived by the prescriber as a lack of faith in them. The first step to facilitating adherence is therefore to take a ‘no-blame approach’ and encourages an honest and open discussion to identify nonadherence and the reasons for nonadherence [1]. Adherence support should be tailored to the needs of the individual addressing perceptions (e.g. necessity beliefs and concerns) as well as practicalities (e.g. capacity and resources). This can be approached in a three stage process: 1) communicating a common-sense rationale for personal need that takes account of the patient’s perceptions of the illness and symptoms expectations and experiences 2) eliciting and addressing specific concerns and 3) making the treatment as convenient and as easy to use a possible. Interventions attempting to improve adherence by applying these approaches have had encouraging results [142,170]. Nonadherence remains a fault-line in clinical practice. Consideration of patients perceptions of treatment necessity and concerns in prescribing and treatment review is essential to support informed choice and optimal adherence to appropriately prescribed treatment.

Supporting Information

Supporting Information S1 PRISMA Checklist. (DOC)

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Author Contributions

Analyzed the data: VC RH RP SC AF NF. Wrote the paper: RH VC RP SC. Conceived and designed the study: RH. Acquired the data: RP SC VC. Critically revised the manuscript for important intellectual content: RH SC RP NF AF VC.

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