

BMJ Open Prevalence and predictors of medication non-adherence among people living with multimorbidity: a systematic review and meta-analysis

Louise Foley ¹, James Larkin,² Richard Lombard-Vance,³ Andrew W Murphy,^{4,5} Lisa Hynes,⁶ Emer Galvin,⁷ Gerard J Molloy¹

To cite: Foley L, Larkin J, Lombard-Vance R, *et al*. Prevalence and predictors of medication non-adherence among people living with multimorbidity: a systematic review and meta-analysis. *BMJ Open* 2021;**11**:e044987. doi:10.1136/bmjopen-2020-044987

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2020-044987>).

Received 21 September 2020
Accepted 06 August 2021



© Author(s) (or their employer(s)) 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to

Louise Foley;
l.foley14@nuigalway.ie

ABSTRACT

Objectives This systematic review aimed to describe medication non-adherence among people living with multimorbidity according to the current literature, and synthesise predictors of non-adherence in this population.

Methods A systematic review was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses. PubMed, EMBASE, CINAHL and PsycINFO were searched for relevant articles published in English language between January 2009 and April 2019. Quantitative studies reporting medication non-adherence and/or predictors of non-adherence among people with two or more chronic conditions were included in the review. A meta-analysis was conducted with a subgroup of studies that used an inclusive definition of multimorbidity to recruit participants, rather than seeking people with specific conditions. Remaining studies reporting prevalence and predictors of non-adherence were narratively synthesised.

Results The database search produced 10 998 records and a further 75 were identified through other sources. Following full-text screening, 178 studies were included in the review. The range of reported non-adherence differed by measurement method, at 76.5% for self-report, 69.4% for pharmacy data, and 44.1% for electronic monitoring. A meta-analysis was conducted with eight studies ($n=8949$) that used an inclusive definition of multimorbidity to recruit participants. The pooled prevalence of non-adherence was 42.6% (95% CI: 34.0 - 51.3%, $k=8$, $I^2=97%$, $p<0.01$). The overall range of non-adherence was 7.0%–83.5%. Frequently reported correlates of non-adherence included previous non-adherence and treatment-related beliefs.

Conclusions The review identified a heterogeneous literature in terms of conditions studied, and definitions and measures of non-adherence used. Results suggest that future attempts to improve adherence among people with multimorbidity should determine for which conditions individuals require most support. The variable levels of medication non-adherence highlight the need for more attention to be paid by healthcare providers to the impact of multimorbidity on chronic disease self-management.

PROSPERO registration number CRD42019133849.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Criteria for inclusion did not specify particular chronic conditions, permitting inclusion of a wide variety of disease combinations.
- ⇒ Studies were not excluded on the basis of design, setting or method of non-adherence measurement, generating a comprehensive overview of the literature.
- ⇒ Due to considerable heterogeneity between studies, meta-analysis and synthesis of predictors was restricted to studies that did not recruit participants with prespecified combinations of conditions.
- ⇒ Quantitative subgroup analysis was not conducted to determine the influence of participant or study characteristics on non-adherence estimates.

INTRODUCTION

Multimorbidity is broadly defined as the coexistence of two or more chronic conditions¹ and has been described as the most common chronic condition experienced by adults.² In a Scottish study of 1.75 million people, the prevalence of multimorbidity was estimated to be 23.3%, increasing to 65% among those aged 65–84 years.³ People living with multimorbidity attend more medical consultations, experience higher rates of hospital admissions, and face increased healthcare costs.⁴ People with multimorbidity are also expected to engage with complex self-management regimens which can include monitoring symptoms, changing lifestyle behaviours, and adhering to prescribed medications.⁵

Adherence refers to the extent to which a person's behaviours correspond with agreed recommendations from their healthcare provider.⁶ Multimorbidity is closely associated with polypharmacy,⁷ and it has been reported previously that the risk of medication non-adherence can increase as people are prescribed more medicines.⁸ The extent of non-adherence among people

with multimorbidity is poorly understood, attributable to challenges in measuring multiple medication adherence.⁹ However, it is recognised that medication non-adherence in multimorbidity can exacerbate the burden experienced by individuals through increased morbidity and mortality.¹⁰ Medication adherence can be influenced by many factors, including treatment characteristics, condition-related factors, and illness and medication beliefs.¹¹ Identifying significant correlates of non-adherence among people self-managing multiple conditions will contribute to an evidence base for developing behavioural treatments which support adherence in the context of multimorbidity.

Much intervention development to improve medication adherence has focused on single-disease populations.¹² Such a focus may produce an artificial underestimation of the complexity of chronic disease self-management when, in reality, most people with a chronic condition have additional morbidity(s).³ This, in turn, may lead to policies and interventions which are not designed with ‘the most common chronic condition’² in mind. In order to develop interventions to improve medication adherence among people living with multimorbidity, it is first necessary to understand the extent of non-adherence in this population, as well as factors that might influence adherence. To our knowledge, a synthesis of the prevalence and predictors of medication non-adherence among people with multimorbidity has not been previously reported. This review therefore aims to (1) describe the prevalence of medication non-adherence among people living with multimorbidity and (2) describe previously identified correlates of non-adherence in this population.

METHODS

A systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement¹³ (online supplemental file 1). The review was prospectively registered on PROSPERO and a peer-reviewed protocol was published.¹⁴ Prior to finalising our aims, we searched in PROSPERO¹⁵ to determine if an equivalent review had been conducted or was currently being conducted.

Inclusion and exclusion criteria

Original peer-reviewed articles and doctoral theses produced in English from 2009 to 2019 were reviewed. A 10-year range was chosen to reflect the marked increase in multimorbidity literature in recent years.¹⁶ Opinion pieces, conference presentations, books, letters, editorials, and abstracts were not reviewed. Quantitative studies including adults aged 18 years or older, living with two or more chronic conditions (including physical and/or mental health conditions) reporting medication non-adherence and/or predictors of non-adherence in an extractable format were considered. Presence of multimorbidity was required to be part of study aims and/or inclusion criteria. Polypharmacy was not used as a

definition of multimorbidity; however, studies referring to use of two or more medications that could be inferred as treatment for two or more chronic conditions were considered. Studies were not excluded based on design, however only observational data were extracted for review. Therefore, clinical trials that did not report baseline non-adherence were excluded. Studies including any participants under 18 years were excluded.

Search strategy and study selection

An electronic database search of PubMed, EMBASE, CINAHL and PsycINFO from January 2009 to April 2019 was conducted using a predefined search strategy combining terms related to ‘multimorbidity’ and ‘medication adherence’ (online supplemental file 2). Reference lists of included studies were screened for relevant articles. Records were exported to EndNote X8 to remove duplicates. Two reviewers (LF, RL-V) each screened 50% of titles and abstracts in Covidence.¹⁷ Twenty per cent of each reviewer’s records were chosen at random for cross-checking by the other reviewer. Studies meeting inclusion criteria were moved forward for full-text screening by two independent reviewers (LF and JL or EG). Where disagreements arose, a third reviewer (GJM or AWM) was consulted.

Data extraction and quality assessment

A data extraction form was developed to extract relevant data from each included study (online supplemental file 3). Where studies reported medication adherence, this was converted to medication *non*-adherence by subtracting the number of adherent participants from the total sample. One reviewer (LF) extracted data from all included studies, and a second reviewer (JL) cross-checked 20%.

The quality of included studies was assessed using criteria for observational studies¹⁸ previously adapted for medication adherence reviews.¹⁹ Criteria include 11 items related to selection methods, measurement, sources of bias, control for confounding, and use of statistics. Each item was answered with ‘yes’, ‘no’, ‘don’t know’ or ‘not applicable’. All included studies were assessed using these criteria, including intervention studies as only baseline observational data were reviewed. One reviewer (LF) assessed the quality of all studies and a second reviewer (EG) cross-checked a random sample of 20%. No studies were excluded based on quality.

Data analysis

Due to between-study heterogeneity relating to study population, design, setting, and measurement and definition of medication non-adherence, a quantitative synthesis involving all studies was not considered appropriate. Meta-analysis was conducted with studies which recruited participants as ‘people living with ≥ 2 chronic conditions’. This group of studies was considered to be most focused in addressing a universal experience of multimorbidity—albeit a multifaceted and complex

experience across individuals—offering results that can be used in future attempts to address non-adherence in this population. Studies which recruited participants with pre-specified conditions were therefore not included in the meta-analysis. Meta-analysis was conducted in R²⁰ using the meta²¹ and metafor²² packages (online supplemental file 4). A random-effects model was used to estimate the pooled prevalence of non-adherence. Between-study heterogeneity was assessed using I^2 .²³

Remaining studies were narratively synthesised to describe medication non-adherence in multimorbidity, informed by Popay and colleagues' guidelines.²⁴ The study characteristics table was preliminarily analysed to identify and count patterns of results. This was followed by an exploration of relationships within and between results of individual studies. Predictors of non-adherence were also synthesised in this way with studies which recruited participants using an inclusive definition of multimorbidity. Predictors were not extracted from studies which recruited participants with pre-specified combinations of diseases due to potential confounding associated with specific conditions, for example, a study of people living with bipolar disorder and depression assessing severity of depressive symptoms and psychological disability as predictors of non-adherence.²⁵

Patient and public involvement

A panel of people with experience of living with multimorbidity were consulted to advise on appropriate methods

for disseminating findings from the review to patients and the public.

RESULTS

Overview of studies

After removing duplicates, 10 998 studies were identified from the database search and 75 from reference lists of included studies. Following screening of titles and abstracts, 449 full-texts were reviewed. Of these, 271 were excluded with reasons (figure 1), with 178 studies included in the final synthesis.^{9 25–201} The study selection process is outlined in the PRISMA flow diagram in figure 1.

Study quality

Results of study quality assessment are summarised in figure 2.

Study characteristics

One hundred and thirty-three studies included participants with ≥ 2 specific conditions, for example, Gibson *et al* recruited participants self-managing type 2 diabetes and hypertension⁷⁹; 26 studies included participants with one specific condition and ≥ 1 other condition(s), for example, Puyat *et al* recruited participants living with depression and an additional chronic health condition¹⁵⁶; and 19 studies recruited participants using an inclusive definition of multimorbidity, for example, Schüz and

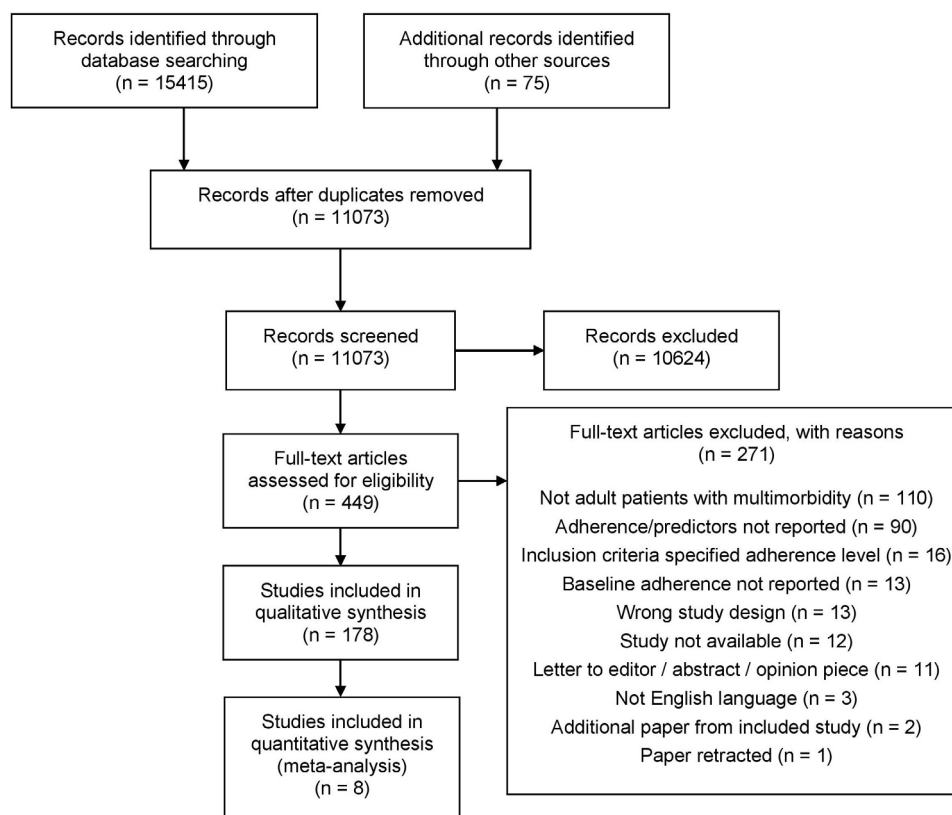


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

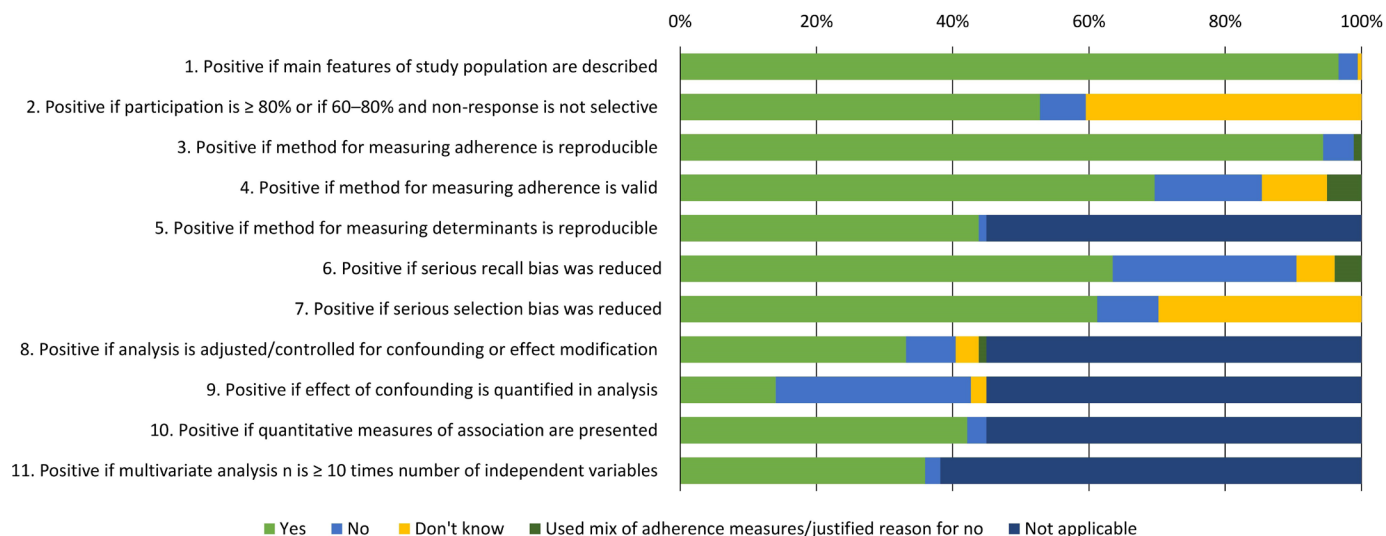


Figure 2 Methodological quality graph.

colleagues¹⁷⁰ recruited people living with ≥ 2 conditions from the Charlson Comorbidity Index²⁰² or Functional Comorbidity Index.²⁰³

Eighty-four studies measured non-adherence using pharmacy data, for example, Kim *et al*¹⁰⁷ used pharmacy claims data to assess non-adherence among people living with hypertension and a psychiatric condition; 81 used self-report, for example, Moore *et al*¹³⁵ measured adherence to medications for HIV and bipolar disorder using a visual analogue scale; and 20 used electronic monitoring, for example, Safren *et al*⁶³ assessed non-adherence to antiretroviral medication among people living with HIV and a depressive mood disorder using a Medication Event Monitoring System (MEMS). Three studies used pill counts,^{59 101 176} two involved reports by a healthcare provider^{80 83} and one did not report the method used.⁶⁴ Ten of these studies used more than one method to measure adherence, for example, Bogner *et al*⁴⁵ used electronic monitoring and self-report to measure non-adherence for diabetes and depression. Forty-seven studies reported average non-adherence only. The characteristics of all included studies are summarised in online supplemental files 5 and 6.

Participant characteristics

The number of participants with multimorbidity in each study ranged from 22¹³⁰ to 599141.²⁰¹ Among 135 studies reporting the mean (SD) age of participants, the average age ranged from 32.4 (9.6)¹⁰⁵ to 80.8 (9.1) years.¹⁵⁸ Ninety-three (52.2%) study samples were majority female, while three studies did not report gender.^{98 117 126}

Prevalence of medication non-adherence

A meta-analysis was conducted with eight studies reporting prevalence of non-adherence and using an inclusive definition of multimorbidity, that is, without seeking people with ≥ 1 specific condition(s).^{56 71 115 137 138 184 189 193} The pooled prevalence of non-adherence was 42.6% (95% CI: 34.0% to 51.3%, $k=8$, $I^2=97\%$, $p<0.01$) (figure 3). The range of non-adherence among studies in the meta-analysis was 16.4%⁷¹–61.4%.¹⁹³ The range among all reviewed studies was 7.0%⁴²–83.5%.¹⁹⁹ Remaining studies were narratively synthesised to describe prevalence and predictors of medication non-adherence.

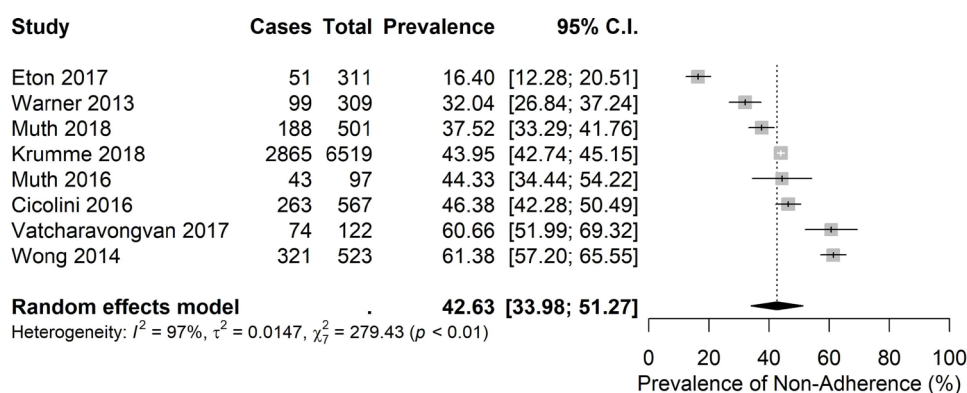


Figure 3 Results of random effects meta-analysis.

Narrative synthesis findings

Medication non-adherence over time

The direction and extent of change in medication non-adherence over time was variable between studies. Among studies reporting prevalence of non-adherence over time, respective lengths of follow-up were three months,⁹⁶ six months,¹⁸⁹ 48 weeks,¹²¹ one year,^{26 36} 16 months,¹⁶¹ two years,⁶⁰ three years,⁴⁸ and five years.¹⁹⁸ Of these, four studies measured change in non-adherence following a recent diagnosis or treatment for an additional condition,^{36 48 96 161} four measured change following medication initiation^{26 60 121 198} and one reported change not related to specific patient or treatment characteristics.¹⁸⁹ Three studies reported decreased non-adherence,^{36 96 161} with the greatest decrease being 9.6% after 3 months.⁹⁶ Four studies reported increased non-adherence,^{26 121 189 198} with the greatest increase being 41.2% after 12 months.²⁶ One study reported variation in how non-adherence changed over time depending on the class of medication,⁶⁰ while another reported an initial 13.9% increase after 2 years, followed by a 14.9% decrease 1 year later.⁴⁸

Assessment of multiple medications

Within individual studies, the extent of non-adherence for one condition did not always correspond with non-adherence for another condition among people taking medications for multimorbidity. Twenty-six studies reported non-adherence prevalence estimates separately for each condition, for example, Foguet-Boreu *et al* reported that, among people living with both diabetes and hypertension, 39.8% were non-adherent to medication for diabetes, while 23.8% were non-adherent to medications for hypertension.⁷⁵ Differences in non-adherence between conditions ranged from 0.8% measured by a 1-item self-report measure in a study of people living with HIV and tuberculosis,¹³⁹ to 33.6% measured by pharmacy data in a study of people with greater non-adherence to medications for Chronic Obstructive Pulmonary Disease (COPD) than depression.²⁷ Four studies reported a difference of $\leq 5\%$,^{45 79 88 139} five reported a difference of 5%–9.9%,^{95 110 129 135 177} eleven reported a difference of 10%–19.9%^{38 57 65 75 84 90 102 133 177 180 191} and six reported a difference of $\geq 20\%$.^{27 66 80 90 105 185}

Physical and mental multimorbidity

Differences in non-adherence between physical and mental health conditions were not consistent across the literature. Among studies of people living with a physical condition and depression and/or anxiety, four reported non-adherence prevalence for both the physical and mental health condition, for example, Gupte-Singh and colleagues reported non-adherence to medications for asthma (62.0%) and depression (74.3%).⁸⁴ Non-adherence was higher for depression in three studies,^{45 84 185} and higher for the physical condition in one study.²⁷

Among studies of people living with a psychiatric condition and a physical condition, seven reported

non-adherence prevalence for both conditions, for example, Moore *et al* reported non-adherence among people living with HIV (52.3%) and bipolar disorder (64.1%).¹³³ Non-adherence was higher for the psychiatric condition in three studies^{90 133 135} and higher for the physical condition in four studies.^{66 88 111 129}

Characteristics of multiple medication regimens

Two studies compared prevalence of non-adherence according to characteristics of multiple medication regimens.^{26 93} Starting medications for two conditions simultaneously resulted in lower non-adherence versus not starting simultaneously (24.8% vs 55.0% at 2 months; 66.0% vs 69.0% at 12 months).²⁶ Hussein and colleagues assessed the difference between a single-pill versus two-pill antihypertensive, lipid-lowering regimen.⁹³ Results concluded that a single-pill regimen improved adherence compared with a two-pill regimen, and improvements were greater among people with previous experience taking either an antihypertensive or lipid-lowering medication.⁹³

Method of non-adherence measurement

Different methods of measuring non-adherence produced differences in the range of non-adherence estimates, with self-report measures producing the widest range, and observed adherence producing the narrowest range. Among 64 studies using pharmacy data, non-adherence prevalence ranged from 10.6% among women with breast cancer and osteoporosis¹⁴⁴ to 80.0% among people with COPD and depression.²⁸ Among 50 studies using self-report, non-adherence prevalence ranged from 7.0% among people with anxiety and cardiac disease⁴² to 83.5% among people with depression and an additional chronic condition(s).¹⁹⁹ Among 10 studies using MEMS, non-adherence prevalence ranged from 20.0% among people living with HIV and hypertension or chronic kidney disease¹⁹¹ to 64.1% among people living with HIV and bipolar disorder.¹³³ Two studies reported prevalence of non-adherence assessed by a healthcare provider⁸³ or a mix of healthcare providers, patients and relatives,⁸⁰ with non-adherence ranging from 8.6%⁸³ to 52.5%.⁸⁰ Two studies used observed medication adherence to identify discrepancies between medications taken and medications prescribed,^{137 138} with non-adherence prevalence ranging from 37.5%¹³⁸ to 44.3%.¹³⁷ among people with three or more chronic conditions. Two studies used pill counts, with non-adherence ranging from 46.3%¹⁰¹ to 70.0%.¹⁷⁶

Nine studies reporting prevalence of non-adherence used more than one measure.^{34 45 51 114 122 137 138 181 194} Among studies using self-report and MEMS, two studies reported lower non-adherence using self-report,^{45 114} one study reported higher non-adherence using self-report¹⁸¹ and one study reported a 1% difference.³⁴ Another study reported no difference between self-report and pharmacy data.⁵¹ Stack and colleagues used self-report to measure prevalence of intentional non-adherence (e.g., deliberately choosing not to take medicines) and unintentional



non-adherence (e.g., forgetting to take medications) to three medications.¹⁷⁷ For each medication, unintentional non-adherence was more prevalent (62.9%, 47.1%, 46.9%) than intentional non-adherence (13.1%, 19.2%, 18.1%).

Predictors of medication (non-)adherence

Eleven studies using an inclusive definition of multimorbidity reported predictors of adherence (see online supplemental file 7).^{40 56 62 71 94 106 168–170 189} Nine used self-report to measure adherence,^{56 62 71 94 106 168–170 189} and two used pharmacy data.^{40 68} The mean age of participants was <65 years in four studies^{40 62 68 94} and >65 in seven studies.^{56 71 106 168–170 189} Five studies assessed demographic variables as predictors,^{56 106 168 169 189} including age, sex, marital status, education and deprivation. No demographic variables significantly predicted non-adherence.

One study assessed health status, which was associated with adherence - that is, poorer health status was associated with stronger motivation to take medications.¹⁰⁶ Other factors assessed included number of prescribed medications,^{56 62 168 169 189} number of chronic conditions,^{62 68 106 168 169} physical fitness¹⁸⁹ and functional health status,¹⁶⁸ as well as presence of other conditions.^{56 68 106} Schüz and colleagues¹⁶⁸ found lower intentional non-adherence among people prescribed more medications and higher intentional non-adherence among people with more conditions; number of conditions and medications did not predict unintentional non-adherence.¹⁶⁸ Domino and colleagues⁶⁸ reported lower non-adherence among those with more comorbidities. Depression was associated with lower adherence, while schizophrenia was linked to both higher and lower adherence, depending on other physical conditions present.⁶⁸

A number of studies explored beliefs about conditions and medications as predictors of adherence. One study reported that better adherence was associated with both stronger necessity beliefs and stronger concern beliefs.⁵⁶ Two studies using the same sample reported more intentional non-adherence among those with increasing beliefs that medications are harmful,¹⁶⁸ and more unintentional non-adherence among those with increasing beliefs that medications are overused.^{168 169} Changes in necessity beliefs predicted intentional non-adherence, with increasing beliefs about necessity associated with improved adherence.^{168 169} Beliefs about consequences, treatment control and timeline were also explored.^{106 170} Kenning and colleagues did not report significant relationships between beliefs and adherence.¹⁰⁶ Schüz and colleagues found higher adherence was predicted by stronger control beliefs, stronger beliefs about negative consequences, and beliefs about a shorter illness timeline.¹⁷⁰ One study assessed beliefs about multimorbidity itself, reporting no significant relationship with adherence.¹⁰⁶

Three studies using the same sample reported an association between previous and later unintentional non-adherence,^{168 169 189} two of which also reported

an association between previous and later intentional non-adherence.^{168 169} Previous medication motivation predicted adherence, with participants with higher motivation at baseline reporting higher adherence at follow-up.¹⁰⁶ Other factors assessed included attitudes towards medications,¹⁸⁹ medication knowledge¹⁰⁶ and medication adherence self-efficacy,⁶² none of which predicted non-adherence. One study assessed general received social support and medication specific-support,¹⁸⁹ with higher medication-specific social support associated with lower adherence; this relationship was moderated by social conflict. General received social support did not predict adherence. Other factors assessed included chronic disease self-efficacy, medication assistance, health literacy and functional health literacy,⁶² none of which predicted non-adherence.

Lower adherence was associated with lower physical ($r = -0.44$) and environmental ($r = -0.57$) quality of life.⁶² Lower prospective memory performance was related to more omission errors of adherence ($r = -0.29$), while lower retrospective memory performance was related to more commission errors ($r = -0.24$).⁹⁴ Other factors positively associated with adherence were medical home enrolment,⁴⁰ better health provider relational quality ($r = 0.22$)⁷¹ and fewer hassles during healthcare system encounters.¹⁰⁶ Self-help behaviours did not predict adherence,¹⁰⁶ better self-monitoring and insight predicted higher motivation to adhere to medications,¹⁰⁶ and a more impulsive/careless problem-solving style was associated with lower adherence ($r = -0.49$).⁶²

DISCUSSION

Our systematic review identified a heterogeneous literature reporting medication non-adherence among people living with multimorbidity. Variation in study design, population, and measurement and definitions of both multimorbidity and non-adherence was observed between studies. Among studies using an inclusive definition of multimorbidity ($k = 11$), correlates of non-adherence included treatment related beliefs and previous non-adherence. From eight studies considered suitable for meta-analysis, 43% (95% CI: 34% - 51%) of participants with multimorbidity were non-adherent to medications. Non-adherence ranged from 16.4%⁷¹ to 61.4%,¹⁹³ with the lowest estimate arising from a single-item self-report measure,⁷¹ and the highest derived from pharmacy data.¹⁹³ One study in the meta-analysis contributed to 76% of the total sample.¹¹⁵ These characteristics of individual studies should be considered when interpreting findings of the quantitative synthesis.

Among studies reporting non-adherence prevalence for more than one condition, results highlighted disparities in non-adherence between conditions. It was previously reported that people with multimorbidity prioritise certain conditions over others,^{204 205} with our results suggesting this prioritisation may be reflected in self-management behaviours. Other factors known to

predict adherence in general may also explain disparities within an individual, including differences in regimen complexity and differences in the expected efficacy of medications.²⁰⁶ Inauen and colleagues⁹ have reported that adherence within an individual can differ between medications, and emphasise the need to assess adherence for multiple medications separately in order to focus interventions appropriately. Despite such calls, a recent systematic review suggested there are no standard criteria for measuring multiple medication adherence, as well as no agreement on how existing measures developed for measuring adherence to monotherapy can be adapted to multiple medications.²⁰⁷ A number of studies reviewed here, including those in the quantitative synthesis, reported a single prevalence estimate representing average non-adherence across conditions, potentially resulting in a concealment of those conditions for which non-adherence is highest. This should be considered when interpreting the meta-analysis.

Among participants with a physical condition and depression, non-adherence was higher for antidepressants in three of four studies. This somewhat supports previous findings that non-adherence to antidepressants is higher than to medications for physical conditions,²⁰⁸ and may extend this observation to instances where both occur in one individual; however, further research is necessary to draw stronger conclusions. Among participants with a psychiatric and physical condition, prevalence of non-adherence to psychiatric medications was higher than non-adherence to medications for physical conditions in three of seven studies. Previous literature has reported that adherence to antipsychotic medications may be lower than adherence to medications for physical conditions,²⁰⁸ while others have found antipsychotic adherence to be higher.²⁰⁹ These discrepancies further highlight the heterogeneity that is inherent in multimorbidity, as well as the importance of considering between-condition medication adherence within individuals. Moreover, it has previously been reported that the condition people with multimorbidity prioritise most can differ over time as conditions and treatments change.²⁰⁵ Considering the cyclical nature of some mental health conditions,²¹⁰ it is important to consider whether self-management behaviours, such as medication taking, fluctuate over time as a result of changing priorities in response to symptoms.

Among the variables frequently tested as predictors were number of chronic conditions and number of prescribed medications. Surprisingly, the strength and direction of association with non-adherence was not consistent across studies. A recent systematic review concluded that deprescribing interventions do not consistently improve adherence,²¹¹ suggesting an equivocal relationship between medication burden and non-adherence. This highlights the clinical dilemma faced by clinicians where deprescribing may be a necessary but not sufficient therapeutic response. It has been suggested previously that the frequency of medication administration has a greater

influence on adherence than number of tablets,²¹² which may have particular relevance in multimorbidity considering some people take medications for different conditions throughout the day while others take multiple medications together.²¹³ Indeed, it has been reported that particular combinations of conditions are associated with higher dosing frequencies in multimorbidity, with potential implications for treatment burden,²¹³ and therefore possibly influencing medication adherence. Mode of drug delivery may also be an influencing factor, with different modes of delivery varying in convenience and, therefore, adherence.²¹⁴ Due to lack of individual patient data regarding treatment regimens, it is beyond the scope of this review to explore this further.

Illness and medication beliefs were among the most frequently explored predictors of adherence. Schüz and colleagues¹⁷⁰ results suggest medication adherence in the context of multimorbidity may be influenced by perceptions of unique conditions as well as the effect of multiple combined illness perceptions. A scale to measure multimorbidity illness perceptions has been developed,²¹⁵ accounting for domains such as treatment burden, emotional impact and prioritisation. When tested within a study reviewed here, this measure did not predict adherence,¹⁰⁶ however, authors note the measure was in early stages of development at the time of administration.¹⁰⁶ Nonetheless, illness perceptions—and how they present in the context of multimorbidity—appear to be of relevance to both intentional and unintentional non-adherence in the context of multimorbidity.^{168–170} This tendency to be influenced by illness beliefs may position intentional non-adherence as a rational judgement for some people self-managing chronic conditions; how this transpires as selective non-adherence among people self-managing multiple conditions should be explored in future research.²¹⁶

Analysis of pharmacy data was the most frequently used method to measure non-adherence, followed by self-report and electronic monitoring. Variation in measurement methods contributed to the heterogeneity that prevented a larger meta-analysis—a limiting factor that has previously been identified in reviews of non-adherence to multiple medications.²¹⁷ While also noting variance due to different combinations of conditions within individual studies, the range of reported non-adherence differed by measurement method (77% for self-report, 69% for pharmacy data, and 44% for MEMS). Results from 10 studies using multiple methods to report prevalence of non-adherence emphasised this variability further, extending to multimorbidity the recommendation to use subjective and objective measures of non-adherence in combination to allow the strengths of each to compensate for the limitations of others.²¹⁸

We did not stratify our analysis of prevalence by age, potentially limiting interpretation of our findings. Notably, age was not found to be a significant correlate in our synthesis of predictors, and it has been suggested previously that there is no consensus on age as a predictor



of non-adherence.²¹⁹ Nevertheless, it may be plausible that variables are differentially associated with non-adherence at different life stages. For example, among reviewed studies, Domino and colleagues⁶⁸ reported lower levels of non-adherence in people with more conditions, with a mean age among participants of 43 years; Schüz and colleagues found higher intentional non-adherence among participants with more conditions, with a mean age of 73 years.¹⁶⁸ Exploring how non-adherence is variably predicted by clinical and psychosocial influences across the lifespan could inform intervention development which is appropriately targeted according to life stage.

The quality assessment produced a number of recommendations for future research exploring non-adherence among people with multimorbidity. Of note, while almost all studies (94%) were judged to have used non-adherence measures that were reproducible, 16% of studies used methods that were not considered to be valid. The validity of non-adherence assessment methods should be a priority for future related investigations. Furthermore, almost 30% of studies were judged not to have reduced serious recall bias. It has been suggested that the appropriate period for retrospective self-report of non-adherence should be balanced between optimising recall and capturing instances of infrequent non-adherence.²²⁰ The optimum recall period for measures of multiple medication non-adherence should be determined.

The methods used to conduct this systematic review have limitations. First, only 20% of titles and abstracts were screened by two reviewers and authors were not contacted for full-text articles or data that was not accessible, both of which increased the risk of excluding relevant studies. Second, criteria for inclusion in the review were limited to English language studies produced between 2009 and 2019. While this date range may exclude relevant articles, the review aimed to synthesise evidence produced since the proliferation of the multimorbidity literature over the last decade,¹⁶ as well as a call for the careful design of adherence research in multimorbidity that uses reliable and consistent adherence measurement and details adherence for multiple conditions.¹² Non-English language articles were not reviewed for feasibility reasons. Third, studies of people with depression or anxiety were eligible for inclusion if the condition was identified through a self-report measure. As a result, it is possible that not all participants had a clinical diagnosis. This decision was made to account for the overrepresentation and underdiagnosis of depression among people with chronic conditions due to incomplete recording in medical records,²²¹ and has been made previously when reviewing the multimorbidity literature.²²² Finally, while the study adopted ‘two or more chronic conditions’ to define multimorbidity, studies were also included if participants were prescribed medications that could be inferred as treatment for a chronic condition. While this extended the definition of multimorbidity beyond clinical diagnoses, to exclude

these studies would have underrepresented the burden that is characteristic of multimorbidity.

CONCLUSION

This review summarises the complexity of non-adherence in multimorbidity, as well as factors that should be considered for the development of interventions to support adherence for ‘the most common chronic condition’. While the review did not identify specific combinations of conditions producing the highest levels of non-adherence, results suggest that non-adherence in multimorbidity varies both between and within studies. Management of multimorbidity demands integration across conditions and clinical guidelines, requiring practitioners and researchers to focus on individual people as opposed to individual diseases.² While the move towards this multi-disease focus is welcomed, attempts by researchers and clinicians to improve medication adherence should determine for which conditions individuals require most support. The use of measures designed to assess multiple medication adherence will be central to achieving this aim.

Author affiliations

¹School of Psychology, National University of Ireland Galway, Galway, Ireland

²HRB Centre for Primary Care Research, Royal College of Surgeons in Ireland, Dublin, Ireland

³Department of Psychology, National University of Ireland Maynooth, Maynooth, Ireland

⁴Discipline of General Practice, National University of Ireland Galway, Galway, Ireland

⁵HRB Primary Care Clinical Trials Network Ireland, National University of Ireland Galway, Galway, Ireland

⁶Health Programmes, Croí Heart & Stroke Centre, Galway, Ireland

⁷School of Pharmacy & Biomolecular Sciences, Royal College of Surgeons in Ireland, Dublin, Ireland

Twitter Louise Foley @louise_foley_ and James Larkin @LarkinJames

Acknowledgements We thank members of the Patient and Public Involvement panel working with the Multimorbidity Collaborative Doctoral Award PhD students for their contribution to plans for disseminating the results of this research to patients and members of the public.

Contributors LF is the guarantor of the review and contributed to study design, data collection, data analysis and original draft preparation. JL, RL-V and EG contributed to data collection and draft review and editing. LH contributed to supervision and draft review and editing. AM and GJM contributed to study design, supervision and draft review and editing.

Funding This research was funded by a Health Research Board Ireland Collaborative Doctoral Award, grant number CDA-2018-003.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. All data relevant to the study are included in the article or uploaded as supplementary information. All data relevant to the study are included in the article, uploaded as supplementary information or deposited on Open Science Framework: <https://osf.io/nym7v/>. Data are available under the terms of the Creative Commons Zero “No rights reserved” data waiver (CCO 1.0 Public domain dedication). Our systematic review produced a large amount of information and the arising database is available for future collaboration on additional analyses. Please contact the corresponding author with any inquiries.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iD

Louise Foley <http://orcid.org/0000-0002-0773-3712>

REFERENCES

- Boyd CM, Fortin M. Future of multimorbidity research: how should understanding of multimorbidity inform health system design? *Public Health Rev* 2010;32:451–74.
- Tinetti ME, Fried TR, Boyd CM. Designing health care for the most common chronic condition--multimorbidity. *JAMA* 2012;307:2493–4.
- Barnett K, Mercer SW, Norbury M, *et al*. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet* 2012;380:37–43.
- Glynn LG, Valderas JM, Healy P, *et al*. The prevalence of multimorbidity in primary care and its effect on health care utilization and cost. *Fam Pract* 2011;28:516–23.
- Bayliss EA, Steiner JF, Fernald DH, *et al*. Descriptions of barriers to self-care by persons with comorbid chronic diseases. *Ann Fam Med* 2003;1:15–21.
- Nieuwlaat R, Wilczynski N, Navarro T, *et al*. Interventions for enhancing medication adherence. *Cochrane Database Syst Rev* 2014:CD000011.
- Payne RA, Avery AJ, Duerden M, *et al*. Prevalence of polypharmacy in a Scottish primary care population. *Eur J Clin Pharmacol* 2014;70:575–81.
- Zelko E, Klemenc-Ketis Z, Tusek-Bunc K. Medication adherence in elderly with polypharmacy living at home: a systematic review of existing studies. *Mater Sociomed* 2016;28:129–32.
- Inauen J, Bierbauer W, Lüscher J, *et al*. Assessing adherence to multiple medications and in daily life among patients with multimorbidity. *Psychol Health* 2017;32:1233–48.
- Simpson SH, Eurich DT, Majumdar SR, *et al*. A meta-analysis of the association between adherence to drug therapy and mortality. *BMJ* 2006;333:15.
- World Health Organization Sabaté E, ed. *Adherence to long-term therapies: evidence for action*. Geneva: World Health Organization, 2003.
- Williams A, Manias E, Walker R. Interventions to improve medication adherence in people with multiple chronic conditions: a systematic review. *J Adv Nurs* 2008;63:132–43.
- Moher D, Liberati A, Tetzlaff J, *et al*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.
- Foley L, Larkin J, Lombard-Vance R, *et al*. Prevalence and predictors of medication non-adherence among patients with multimorbidity: a systematic review protocol. *HRB Open Res* 2019;2:29.
- Booth A, Clarke M, Dooley G, *et al*. The nuts and bolts of PROSPERO: an international prospective register of systematic reviews. *Syst Rev* 2012;1:2.
- Xu X, Mishra GD, Jones M. Mapping the global research landscape and knowledge gaps on multimorbidity: a bibliometric study. *J Glob Health* 2017;7:010414.
- Veritas Health Innovation. Covidence systematic review software. Melbourne, Australia; 2020.
- Sanderson S, Tatt ID, Higgins JPT. Tools for assessing quality and susceptibility to bias in observational studies in epidemiology: a systematic review and annotated bibliography. *Int J Epidemiol* 2007;36:666–76.
- Pasma A, van't Spijker A, Hazes JMW, *et al*. Factors associated with adherence to pharmaceutical treatment for rheumatoid arthritis patients: a systematic review. *Semin Arthritis Rheum* 2013;43:18–28.
- R Core Team. R: a language and environment for statistical computing, 2017. Available: <https://www.R-project.org/>
- Schwarzer G. General package for meta-analysis, 2020. Available: <http://meta-analysis-with-r.org>
- Viecthbauer W. Conducting meta-analyses in R with the metafor package. *J Stat Softw* 2010;36:1–48.
- Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539–58.
- Popay J, Roberts H, Sowden A. *Guidance on the conduct of narrative synthesis in systematic reviews. A product from the ESRC methods programme*. Lancaster: Insiute of Health Research, 2006.
- Gaudiano BA, Wenze SJ, Weinstock LM, *et al*. Valued living and its relationship to medication adherence in patients with bipolar and comorbid substance use disorders. *J Nerv Ment Dis* 2017;205:178–81.
- Agarwal S, Tang SSK, Rosenberg N, *et al*. Does synchronizing initiation of therapy affect adherence to concomitant use of antihypertensive and lipid-lowering therapy? *Am J Ther* 2009;16:119–26.
- Albrecht JS, Khokhar B, Huang T-Y, *et al*. Adherence and healthcare utilization among older adults with COPD and depression. *Respir Med* 2017;129:53–8.
- Albrecht JS, Park Y, Hur P, *et al*. Adherence to maintenance medications among older adults with chronic obstructive pulmonary disease. The role of depression. *Ann Am Thorac Soc* 2016;13:1497–504.
- An J, Nichol MB. Multiple medication adherence and its effect on clinical outcomes among patients with comorbid type 2 diabetes and hypertension. *Med Care* 2013;51:879–87.
- Applebaum AJ, Reilly LC, Gonzalez JS, *et al*. The impact of neuropsychological functioning on adherence to HAART in HIV-infected substance abuse patients. *AIDS Patient Care STDS* 2009;23:455–62.
- Applebaum AJ, Richardson MA, Brady SM, *et al*. Gender and other psychosocial factors as predictors of adherence to highly active antiretroviral therapy (HAART) in adults with comorbid HIV/AIDS, psychiatric and substance-related disorder. *AIDS Behav* 2009;13:60–5.
- Axon RN, Gebregziabher M, Hunt KJ, *et al*. Comorbid depression is differentially associated with longitudinal medication nonadherence by race/ethnicity in patients with type 2 diabetes. *Medicine* 2016;95:e3983.
- Baca-García E, Sher L, Perez-Rodriguez MM, *et al*. Treatment of depressed bipolar patients with alcohol use disorders: plenty of room for improvement. *J Affect Disord* 2009;115:262–8.
- Badiee J, Riggs PK, Rooney AS, *et al*. Approaches to identifying appropriate medication adherence assessments for HIV infected individuals with comorbid bipolar disorder. *AIDS Patient Care STDS* 2012;26:388–94.
- Baik SH, Rollman BL, Reynolds CF, *et al*. The effect of the US Medicare Part D coverage gaps on medication use among patients with depression and heart failure. *J Ment Health Policy Econ* 2012;15:105–18.
- Banegas MP, Emerson MA, Adams AS, *et al*. Patterns of medication adherence in a multi-ethnic cohort of prevalent statin users diagnosed with breast, prostate, or colorectal cancer. *J Cancer Surviv* 2018;12:794–802.
- Basak RS. *Concurrent adherence to multiple chronic disease medications: examining the behavior and issues concerning its measurement*. 2013;Doctorate Degree.
- Batchelder AW, Gonzalez JS, Berg KM. Differential medication nonadherence and illness beliefs in co-morbid HIV and type 2 diabetes. *J Behav Med* 2014;37:266–75.
- Bauer AM, Schillinger D, Parker MM, *et al*. Health literacy and antidepressant medication adherence among adults with diabetes: the diabetes study of northern California (distance). *J Gen Intern Med* 2013;28:1181–7.
- Beadles CA, Farley JF, Ellis AR, *et al*. Do medical homes increase medication adherence for persons with multiple chronic conditions? *Med Care* 2015;53:168–76.
- Benner JS, Chapman RH, Petrilla AA, *et al*. Association between prescription burden and medication adherence in patients initiating antihypertensive and lipid-lowering therapy. *Am J Health Syst Pharm* 2009;66:1471–7.
- Berg SK, Rasmussen TB, Thrysoe L, *et al*. Mental health is a risk factor for poor outcomes in cardiac patients: findings from the National DenHeart survey. *J Psychosom Res* 2018;112:66–72.

- 43 Biftu BB, Dachew BA, Tiruneh BT, *et al.* Depression among people with epilepsy in Northwest Ethiopia: a cross-sectional institution based study. *BMC Res Notes* 2015;8:585.
- 44 Blashill AJ, Bedoya CA, Mayer KH, *et al.* Psychosocial syndemics are additively associated with worse art adherence in HIV-infected individuals. *AIDS Behav* 2015;19:981–6.
- 45 Bogner HR, de Vries HF, O'Donnell AJ, *et al.* Measuring concurrent oral hypoglycemic and antidepressant adherence and clinical outcomes. *Am J Manag Care* 2013;19:e85–92.
- 46 Cabrera-Marroquín R, Contreras-Yáñez I, Alcocer-Castillejos N, *et al.* Major depressive episodes are associated with poor concordance with therapy in rheumatoid arthritis patients: the impact on disease outcomes. *Clin Exp Rheumatol* 2014;32:904–13.
- 47 Calderón-Larrañaga A, Diaz E, Poblador-Plou B, *et al.* Non-adherence to antihypertensive medication: the role of mental and physical comorbidity. *Int J Cardiol* 2016;207:310–6.
- 48 Calip GS, Boudreau DM, Loggers ET. Changes in adherence to statins and subsequent lipid profiles during and following breast cancer treatment. *Breast Cancer Res Treat* 2013;138:225–33.
- 49 Calip GS, Hubbard RA, Stergachis A, *et al.* Adherence to oral diabetes medications and glycemic control during and following breast cancer treatment. *Pharmacoepidemiol Drug Saf* 2015;24:75–85.
- 50 Calip GS, Elmore JG, Boudreau DM. Characteristics associated with nonadherence to medications for hypertension, diabetes, and dyslipidemia among breast cancer survivors. *Breast Cancer Res Treat* 2017;161:161–72.
- 51 Cantudo-Cuenca MR, Jiménez-Galán R, Almeida-González CV, *et al.* Concurrent use of comedications reduces adherence to antiretroviral therapy among HIV-infected patients. *J Manag Care Spec Pharm* 2014;20:844–50.
- 52 Casaletto KB, Kwan S, Montoya JL, *et al.* Predictors of psychotropic medication adherence among HIV+ individuals living with bipolar disorder. *Int J Psychiatry Med* 2016;51:69–83.
- 53 Caughey GE, Preiss AK, Vitry AI, *et al.* Does antidepressant medication use affect persistence with diabetes medicines? *Pharmacoepidemiol Drug Saf* 2013;22:615–22.
- 54 Cha E, Clark PC, Reilly CM, *et al.* Educational needs for improving self-care in heart failure patients with diabetes. *Diabetes Educ* 2012;38:673–84.
- 55 Chou Y-T, Winn AN, Rosenstein DL, *et al.* Assessing disruptions in adherence to antidepressant treatments after breast cancer diagnosis. *Pharmacoepidemiol Drug Saf* 2017;26:676–84.
- 56 Cicolini G, Comparcini D, Flacco ME, *et al.* Self-Reported medication adherence and beliefs among elderly in multi-treatment: a cross-sectional study. *Appl Nurs Res* 2016;30:131–6.
- 57 Crowley MJ, Bosworth HB, Coffman CJ, *et al.* Tailored case management for diabetes and hypertension (TEACH-DM) in a community population: study design and baseline sample characteristics. *Contemp Clin Trials* 2013;36:298–306.
- 58 Crowley MJ, Zullig LL, Shah BR, *et al.* Medication non-adherence after myocardial infarction: an exploration of modifying factors. *J Gen Intern Med* 2015;30:83–90.
- 59 Cruess DG, Kalichman SC, Amaral C, *et al.* Benefits of adherence to psychotropic medications on depressive symptoms and antiretroviral medication adherence among men and women living with HIV/AIDS. *Ann Behav Med* 2012;43:189–97.
- 60 Cziraky MJ, Reddy VS, Luthra R, *et al.* Clinical outcomes and medication adherence in acute coronary syndrome patients with and without type 2 diabetes mellitus: a longitudinal analysis 2006–2011. *J Manag Care Spec Pharm* 2015;21:470–7.
- 61 Daniali SS, Mostafavi Darani F, Tavassoli E. The prevalence of depression and its association with self-management behaviors in chronic disease patients. *Iran J Psychiatry* 2018;13:e10161.
- 62 Daniels LM. Improving medication adherence in patients with multiple chronic conditions: evaluation of a pilot intervention in a rural primary care clinic, 2015. Available: <https://thescholarship.ecu.edu/handle/10342/4989>
- 63 Davies ML, Johnson MD, Brown JN, *et al.* Predictors of glycaemic control among HIV-positive veterans with diabetes. *Int J STD AIDS* 2015;26:262–7.
- 64 Davis EM, Appel LJ, Wang X, *et al.* Limitations of analyses based on achieved blood pressure: lessons from the African American study of kidney disease and hypertension trial. *Hypertension* 2011;57:1061–8.
- 65 De Leon SF, Pauls L, Arya V, *et al.* Effect of physician participation in a multi-element health information and data exchange program on chronic illness medication adherence. *J Am Board Fam Med* 2015;28:742–9.
- 66 Desai PR, Adeyemi AO, Richards KM, *et al.* Adherence to oral diabetes medications among users and nonusers of antipsychotic medication. *Psychiatr Serv* 2014;65:215–20.
- 67 Dhamane AD, Schwab P, Hopson S, *et al.* Association between adherence to medications for COPD and medications for other chronic conditions in COPD patients. *Int J Chron Obstruct Pulmon Dis* 2017;12:115–22.
- 68 Domino ME, Beadles CA, Lichstein JC, *et al.* Heterogeneity in the quality of care for patients with multiple chronic conditions by psychiatric comorbidity. *Med Care* 2014;52 Suppl 3:S101–9.
- 69 Druss BG, Zhao L, von Esenwein SA, *et al.* The health and recovery peer (HARP) program: a peer-led intervention to improve medical self-management for persons with serious mental illness. *Schizophr Res* 2010;118:264–70.
- 70 DuChane J, Clark B, Hou J, *et al.* Impact of HIV-specialized pharmacies on adherence to medications for comorbid conditions. *J Am Pharm Assoc* 2014;54:493–501.
- 71 Eton DT, Ridgeway JL, Linzer M, *et al.* Healthcare provider relational quality is associated with better self-management and less treatment burden in people with multiple chronic conditions. *Patient Prefer Adherence* 2017;11:1635–46.
- 72 Farley JF, Hansen RA, Yu-Isenberg KS, *et al.* Antipsychotic adherence and its correlation to health outcomes for chronic comorbid conditions. *Prim Care Companion CNS Disord* 2012;14:m01324.
- 73 Feldman JM, Matte L, Interian A, *et al.* Psychological treatment of comorbid asthma and panic disorder in Latino adults: results from a randomized controlled trial. *Behav Res Ther* 2016;87:142–54.
- 74 Ferguson C, Inglis SC, Newton PJ, *et al.* Multi-morbidity, frailty and self-care: important considerations in treatment with anticoagulation drugs. outcomes of the AFASTER study. *Eur J Cardiovasc Nurs* 2017;16:113–24.
- 75 Foguet-Boreu Q, Violán C, López Jiménez T, *et al.* Pharmacological control of diabetes and hypertension comorbidity in the elderly: A study of "real world" data. *Prim Care Diabetes* 2017;11:348–59.
- 76 Gathright EC, Dolansky MA, Gunstad J, *et al.* The impact of medication nonadherence on the relationship between mortality risk and depression in heart failure. *Health Psychol* 2017;36:839–47.
- 77 Gaynes BN, O'Donnell J, Nelson E, *et al.* Psychiatric comorbidity in depressed HIV-infected individuals: common and clinically consequential. *Gen Hosp Psychiatry* 2015;37:277–82.
- 78 Gentil L, Vasiliadis H-M, Prévillé M. Adherence to oral antihyperglycemic agents among older adults with mental disorders and its effect on health care costs, Quebec, Canada, 2005–2008. *Prev Chronic Dis* 2019;12:150412.
- 79 Gibson DS, Nathan AG, Quinn MT, *et al.* Patient expectations of hypertension and diabetes medication: excessive focus on short-term benefits. *SAGE Open Med* 2018;6:1–7.
- 80 Gnanasan S, Ting KN, Wong KT, *et al.* Convergence of tuberculosis and diabetes mellitus: time to individualise pharmaceutical care. *Int J Clin Pharm* 2011;33:44–52.
- 81 Gonzalez JS, Psaros C, Batchelder A, *et al.* Clinician-assessed depression and HAART adherence in HIV-infected individuals in methadone maintenance treatment. *Ann Behav Med* 2011;42:120–6.
- 82 Grove LR, Olesiuk WJ, Ellis AR, *et al.* Evaluating the potential for primary care to serve as a mental health home for people with schizophrenia. *Gen Hosp Psychiatry* 2017;47:14–19.
- 83 Gundling F, Seidl H, Strassen I, *et al.* Clinical manifestations and treatment options in patients with cirrhosis and diabetes mellitus. *Digestion* 2013;87:75–84.
- 84 Gupte-Singh K, Kim G, Barner JC. Impact of comorbid depression on medication adherence and asthma-related healthcare costs in Texas Medicaid patients with asthma. *J Pharm Health Serv Res* 2015;6:197–205.
- 85 Halava H, Korhonen MJ, Huupponen R, *et al.* Lifestyle factors as predictors of nonadherence to statin therapy among patients with and without cardiovascular comorbidities. *CMAJ* 2014;186:E449–56.
- 86 Han Y. Medication adherence outcomes in elderly patients with hypertension and chronic kidney disease: a geographical approach, 2017. Available: <https://deepblue.lib.umich.edu/handle/2027.42/137046>
- 87 Hansen RA, Dusetzina SB, Song L, *et al.* Depression affects adherence measurement but not the effectiveness of an adherence intervention in heart failure patients. *J Am Pharm Assoc* 2009;49:760–8.
- 88 Hansen RA, Maciejewski M, Yu-Isenberg K, *et al.* Adherence to antipsychotics and cardiometabolic medication: association with health care utilization and costs. *Psychiatr Serv* 2012;63:920–8.

- 89 Hansen RA, Voils CI, Farley JF, *et al.* Prescriber continuity and medication adherence for complex patients. *Ann Pharmacother* 2015;49:293–302.
- 90 Hansen RA, Hohmann N, Maciejewski ML, *et al.* Continuity of medication management among adults with schizophrenia and comorbid cardiometabolic conditions. *J Pharm Health Serv Res* 2018;9:13–20.
- 91 Hapangama A, Kuruppuarachchi KALA, Pathmeswaran A. Substance use disorders among mentally ill patients in a General Hospital in Sri Lanka: prevalence and correlates. *Ceylon Med J* 2013;58:111–5.
- 92 Hawke LD, Velyvis V, Parikh SV. Bipolar disorder with comorbid anxiety disorders: impact of comorbidity on treatment outcome in cognitive-behavioral therapy and psychoeducation. *Int J Bipolar Disord* 2013;1:15.
- 93 Hussein MA, Chapman RH, Benner JS. Does a single-pill antihypertensive/lipid-lowering regimen improve adherence in US managed care enrollees? *Am J Cardiovasc Drugs* 2010;10:193–202.
- 94 Ihle A, Inauen J, Scholz U, *et al.* Prospective and retrospective memory are differentially related to self-rated omission and commission errors in medication adherence in multimorbidity. *Appl Neuropsychol Adult* 2017;24:505–11.
- 95 Iyengar RN, LeFrancois AL, Henderson RR, *et al.* Medication nonadherence among Medicare beneficiaries with comorbid chronic conditions: influence of pharmacy dispensing channel. *J Manag Care Spec Pharm* 2016;22:550–60.
- 96 James J, Harris YT, Kronish IM, *et al.* Exploratory study of impact of cancer-related posttraumatic stress symptoms on diabetes self-management among cancer survivors. *Psychooncology* 2018;27:648–53.
- 97 Jaworski F, Dubertret C, Adès J, *et al.* Presence of co-morbid substance use disorder in bipolar patients worsens their social functioning to the level observed in patients with schizophrenia. *Psychiatry Res* 2011;185:129–34.
- 98 Jing S, Naliboff A, Kaufman MB, *et al.* Descriptive analysis of mail interventions with physicians and patients to improve adherence with antihypertensive and antidiabetic medications in a mixed-model managed care organization of commercial and Medicare members. *J Manag Care Pharm* 2011;17:355–66.
- 99 Joseph N, Yogananda R, Padman V. A study on prescription pattern of antihypertensive agents in chronic renal failure patients and assessment of medication adherence. *Int J Pharm Sci Rev Res* 2017;45:72–5.
- 100 Kacanek D, Jacobson DL, Spiegelman D, *et al.* Incident depression symptoms are associated with poorer HAART adherence: a longitudinal analysis from the nutrition for healthy living study. *J Acquir Immune Defic Syndr* 2010;53:266–72.
- 101 Kalichman SC, Pellowski J, Kegler C, *et al.* Medication adherence in people dually treated for HIV infection and mental health conditions: test of the medications beliefs framework. *J Behav Med* 2015;38:632–41.
- 102 Kamal S, Bugnon O, Cavassini M, *et al.* HIV-Infected patients' beliefs about their chronic co-treatments in comparison with their combined antiretroviral therapy. *HIV Med* 2018;19:49–58.
- 103 Katerndahl D, Calmbach WL, Becho J. Effect of comorbid depression on outcomes in diabetes and its relationship to quality of care and patient adherence: a statewide primary care ambulatory research and resources consortium study. *Prim Care Companion CNS Disord* 2012;14:m01269.
- 104 Katon W, Russo J, Lin EHB, *et al.* Diabetes and poor disease control: is comorbid depression associated with poor medication adherence or lack of treatment intensification? *Psychosom Med* 2009;71:965–72.
- 105 Kebede A, Wabe NT. Medication adherence and its determinants among patients on concomitant tuberculosis and antiretroviral therapy in South West Ethiopia. *N Am J Med Sci* 2012;4:67–71.
- 106 Kenning C, Fisher L, Bee P, *et al.* Primary care practitioner and patient understanding of the concepts of multimorbidity and self-management: a qualitative study. *SAGE Open Med* 2013;1:205031211351000.
- 107 Kim HK, Park JH, Park JH, *et al.* Differences in adherence to antihypertensive medication regimens according to psychiatric diagnosis: results of a Korean population-based study. *Psychosom Med* 2010;72:80–7.
- 108 Kong MC, Nahata MC, Lacombe VA, *et al.* Association between race, depression, and antiretroviral therapy adherence in a low-income population with HIV infection. *J Gen Intern Med* 2012;27:1159–64.
- 109 Kostev K, Jacob L. Association between depression and persistence with oral antihyperglycemic drugs in type 2 diabetes mellitus patients in Germany. *Psychiatry Res* 2018;261:90–3.
- 110 Kreyenbuhl J, Dixon LB, McCarthy JF, *et al.* Does adherence to medications for type 2 diabetes differ between individuals with vs without schizophrenia? *Schizophr Bull* 2010;36:428–35.
- 111 Kreyenbuhl J, Leith J, Medoff DR, *et al.* A comparison of adherence to hypoglycemic medications between type 2 diabetes patients with and without serious mental illness. *Psychiatry Res* 2011;188:109–14.
- 112 Krivoy A, Balicer RD, Feldman B, *et al.* Adherence to antidepressant therapy and mortality rates in ischaemic heart disease: cohort study. *Br J Psychiatry* 2015;206:297–301.
- 113 Krivoy A, Stubbs B, Balicer RD, *et al.* Low adherence to antidepressants is associated with increased mortality following stroke: a large nationally representative cohort study. *Eur Neuropsychopharmacol* 2017;27:970–6.
- 114 Krousel-Wood M, Islam T, Muntner P, *et al.* Association of depression with antihypertensive medication adherence in older adults: cross-sectional and longitudinal findings from CoSMO. *Ann Behav Med* 2010;40:248–57.
- 115 Krumme AA, Glynn RJ, Schneeweiss S, *et al.* Medication synchronization programs improve adherence to cardiovascular medications and health care use. *Health Aff* 2018;37:125–33.
- 116 Kumar V, Encinosa W. Effects of antidepressant treatment on antiretroviral regimen adherence among depressed HIV-infected patients. *Psychiatr Q* 2009;80:131–41.
- 117 Langness J, Cook PF, Gill J, *et al.* Comparison of adherence rates for antiretroviral, blood pressure, or mental health medications for HIV-positive patients at an academic medical center outpatient pharmacy. *J Manag Care Spec Pharm* 2014;20:809–14.
- 118 Lee S, Rothbard AB, Noll E, *et al.* Use of HIV and psychotropic medications among persons with serious mental illness and HIV/AIDS. *Adm Policy Ment Health* 2011;38:335–44.
- 119 Li YT, Wang HHX, Liu KQL, *et al.* Medication adherence and blood pressure control among hypertensive patients with coexisting long-term conditions in primary care settings: a cross-sectional analysis. *Medicine* 2016;95:e3572.
- 120 Lin EHB, Von Korff M, Ciechanowski P, *et al.* Treatment adjustment and medication adherence for complex patients with diabetes, heart disease, and depression: a randomized controlled trial. *Ann Fam Med* 2012;10:6–14.
- 121 Lo Re V, Teal V, Localio AR, *et al.* Adherence to hepatitis C virus therapy in HIV/hepatitis C-coinfected patients. *AIDS Behav* 2013;17:94–103.
- 122 Long JA, Wang A, Medvedeva EL, *et al.* Glucose control and medication adherence among veterans with diabetes and serious mental illness: does collocation of primary care and mental health care matter? *Diabetes Care* 2014;37:2261–7.
- 123 Lunghi C, Zongo A, Moisan J, *et al.* Factors associated with antidiabetic medication non-adherence in patients with incident comorbid depression. *J Diabetes Complications* 2017;31:1200–6.
- 124 Magidson JF. Mediators of the relationship between depression and medication adherence among HIV positive substance users 2012.
- 125 Manuel JI, Covell NH, Jackson CT, *et al.* Does assertive community treatment increase medication adherence for people with co-occurring psychotic and substance use disorders? *J Am Psychiatr Nurses Assoc* 2011;17:51–6.
- 126 Mathew EM, Rajiah K. Assessment of medication adherence in type-2 diabetes patients on poly pharmacy and the effect of patient counseling given to them in a Multispecialty Hospital. *J Basic Clin Pharm* 2013;5:15–18.
- 127 May HT, Sheng X, Catinella AP, *et al.* Antilipidemic adherence post-coronary artery disease diagnosis among those with and without an ICD-9 diagnosis of depression. *J Psychosom Res* 2010;69:169–74.
- 128 McCusker J, Lambert SD, Cole MG, *et al.* Activation and self-efficacy in a randomized trial of a depression self-care intervention. *Health Educ Behav* 2016;43:716–25.
- 129 Mellins CA, Havens JF, McDonnell C, *et al.* Adherence to antiretroviral medications and medical care in HIV-infected adults diagnosed with mental and substance abuse disorders. *AIDS Care* 2009;21:168–77.
- 130 Miketic JK. Diabetic coronary heart patients' adherence to cardiac rehabilitation programs 2011.
- 131 Mira JJ, Navarro I, Botella F, *et al.* A Spanish pillbox app for elderly patients taking multiple medications: randomized controlled trial. *J Med Internet Res* 2014;16:e99.
- 132 Monroe AK, Pena JS, Moore RD, *et al.* Randomized controlled trial of a pictorial aid intervention for medication adherence among HIV-positive patients with comorbid diabetes or hypertension. *AIDS Care* 2018;30:199–206.
- 133 Moore DJ, Posada C, Parikh M, *et al.* HIV-Infected individuals with co-occurring bipolar disorder evidence poor antiretroviral and psychiatric medication adherence. *AIDS Behav* 2012;16:2257–66.

- 134 Moore DJ, Blackstone K, Woods SP, *et al.* Methamphetamine use and neuropsychiatric factors are associated with antiretroviral non-adherence. *AIDS Care* 2012;24:1504–13.
- 135 Moore DJ, Poquette A, Casaletto KB, *et al.* Individualized Texting for adherence building (ITAB): improving antiretroviral dose timing among HIV-infected persons with co-occurring bipolar disorder. *AIDS Behav* 2015;19:459–71.
- 136 Muntner P, Judd SE, Krousel-Wood M, *et al.* Low medication adherence and hypertension control among adults with CKD: data from the REGARDS (reasons for geographic and racial differences in stroke) study. *Am J Kidney Dis* 2010;56:447–57.
- 137 Muth C, Harder S, Uhlmann L, *et al.* Pilot study to test the feasibility of a trial design and complex intervention on prioritising MULTImedication in multimorbidity in general practices (PRIMUMpilot). *BMJ Open* 2016;6:e011613.
- 138 Muth C, Uhlmann L, Haefeli WE, *et al.* Effectiveness of a complex intervention on prioritising MULTImedication in multimorbidity (primum) in primary care: results of a pragmatic cluster randomised controlled trial. *BMJ Open* 2018;8:e017740.
- 139 Naidoo P, Peltzer K, Louw J, *et al.* Predictors of tuberculosis (TB) and antiretroviral (ARV) medication non-adherence in public primary care patients in South Africa: a cross sectional study. *BMC Public Health* 2013;13:396.
- 140 Nakimuli-Mpungu E, Musisi S, Wamala K, *et al.* Recruitment and baseline characteristics of participants in the social, emotional, and economic empowerment through knowledge of group support psychotherapy study (SEEK-GSP): cluster randomized controlled trial. *JMIR Res Protoc* 2019;8:e11560.
- 141 Natarajan N, Putnam W, Van Aarsen K, *et al.* Adherence to antihypertensive medications among family practice patients with diabetes mellitus and hypertension. *Can Fam Physician* 2013;59:e93–100.
- 142 Nelson LA, Graham MR, Lindsey CC, *et al.* Adherence to antihyperlipidemic medication and lipid control in diabetic Veterans Affairs patients with psychotic disorders. *Psychosomatics* 2011;52:310–8.
- 143 Nelson LA, Graham MR, Lindsey CC, *et al.* Medication adherence and glycemic control in patients with psychotic disorders in the Veterans Affairs healthcare system. *Pharm Pract* 2011;9:57–65.
- 144 Neugut AI, Zhong X, Wright JD, *et al.* Nonadherence to medications for chronic conditions and nonadherence to adjuvant hormonal therapy in women with breast cancer. *JAMA Oncol* 2016;2:1326–32.
- 145 Newville H, Berg KM, Gonzalez JS. The interaction of active substance use, depression, and antiretroviral adherence in methadone maintenance. *Int J Behav Med* 2015;22:214–22.
- 146 Nichol MB, Knight TK, Wu J, *et al.* Transition probabilities and predictors of adherence in a California Medicaid population using antihypertensive and lipid-lowering medications. *Value Health* 2009;12:544–50.
- 147 Otenyo S, Maranga A. Factors affecting adherence to anti-hypertensive medication regimen among hemodialysis patients attending a private hospital Mombasa, Kenya. *Int J Pharm Sci Res* 2018;9:755–60.
- 148 Owen-Smith A, Stewart C, Green C, *et al.* Adherence to common cardiovascular medications in patients with schizophrenia vs. patients without psychiatric illness. *Gen Hosp Psychiatry* 2016;38:9–14.
- 149 Padman V, Yogananda R, Bharathi D. A study on prescription pattern of oral hypoglycemic agents and insulin therapy in chronic renal failure patients and assessment of medication adherence. *Int J Pharm Sci Res* 2017;45:68–71.
- 150 Pantalone DW, Hessler DM, Bankoff SM, *et al.* Psychosocial correlates of HIV-monoinfection and HIV/HCV-coinfection among men who have sex with men. *J Behav Med* 2012;35:520–8.
- 151 Parpouchi M, Moniruzzaman A, Rezansoff SN, *et al.* Characteristics of adherence to methadone maintenance treatment over a 15-year period among homeless adults experiencing mental illness. *Addict Behav Rep* 2017;6:106–11.
- 152 Patel I, Erickson SR, Caldwell CH, *et al.* Predictors of medication adherence and persistence in Medicaid enrollees with developmental disabilities and type 2 diabetes. *Res Social Adm Pharm* 2016;12:592–603.
- 153 Pence BW, Gaynes BN, Adams JL, *et al.* The effect of antidepressant treatment on HIV and depression outcomes: results from a randomized trial. *AIDS* 2015;29:1975–86.
- 154 Pentakota SR. Impact of chronic comorbid illnesses on diabetes care among veterans with type 2 diabetes mellitus 2013.
- 155 Poon I, Lal LS, Ford ME, *et al.* Racial/Ethnic disparities in medication use among veterans with hypertension and dementia: a national cohort study. *Ann Pharmacother* 2009;43:185–93.
- 156 Puyat JH, Kazanjian A, Wong H, *et al.* Comorbid chronic general health conditions and depression care: a population-based analysis. *Psychiatr Serv* 2017;68:907–15.
- 157 Qian J, Simoni-Wastila L, Rattinger GB, *et al.* Association between depression and maintenance medication adherence among Medicare beneficiaries with chronic obstructive pulmonary disease. *Int J Geriatr Psychiatry* 2014;29:49–57.
- 158 Rattinger GB, Dutcher SK, Chhabra PT, *et al.* The effect of dementia on medication use and adherence among Medicare beneficiaries with chronic heart failure. *Am J Geriatr Pharmacother* 2012;10:69–80.
- 159 Reed RL, Roeger L, Howard S, *et al.* A self-management support program for older Australians with multiple chronic conditions: a randomised controlled trial. *Med J Aust* 2018;208:69–74.
- 160 Rosenblum A, Matusow H, Fong C, *et al.* Efficacy of dual focus mutual aid for persons with mental illness and substance misuse. *Drug Alcohol Depend* 2014;135:78–87.
- 161 Roux P, Fugon L, Winnock M, *et al.* Positive impact of hepatitis C virus (HCV) treatment on antiretroviral treatment adherence in human immunodeficiency virus-HCV coinfecting patients: one more argument for expanded access to HCV treatment for injecting drug users. *Addiction* 2012;107:152–9.
- 162 Saadat Z, Nikdoust F, Aerab-Sheibani H, *et al.* Adherence to antihypertensives in patients with comorbid condition. *Nephrourol Mon* 2015;7:e29863.
- 163 Safren SA, O'Cleirigh C, Tan JY, *et al.* A randomized controlled trial of cognitive behavioral therapy for adherence and depression (CBT-AD) in HIV-infected individuals. *Health Psychol* 2009;28:1–10.
- 164 Safren SA, O'Cleirigh CM, Bullis JR, *et al.* Cognitive behavioral therapy for adherence and depression (CBT-AD) in HIV-infected injection drug users: a randomized controlled trial. *J Consult Clin Psychol* 2012;80:404–15.
- 165 Safren SA, Gonzalez JS, Wexler DJ, *et al.* A randomized controlled trial of cognitive behavioral therapy for adherence and depression (CBT-AD) in patients with uncontrolled type 2 diabetes. *Diabetes Care* 2014;37:625–33.
- 166 Santorelli ML, Steinberg MB, Hirshfield KM, *et al.* Effects of breast cancer on chronic disease medication adherence among older women. *Pharmacoepidemiol Drug Saf* 2016;25:898–907.
- 167 Schmitt KE, Edie CF, Laflam P, *et al.* Adherence to antihypertensive agents and blood pressure control in chronic kidney disease. *Am J Nephrol* 2010;32:541–8.
- 168 Schüz B, Wurm S, Ziegelmann JP, *et al.* Changes in functional health, changes in medication beliefs, and medication adherence. *Health Psychol* 2011;30:31–9.
- 169 Schüz B, Marx C, Wurm S, *et al.* Medication beliefs predict medication adherence in older adults with multiple illnesses. *J Psychosom Res* 2011;70:179–87.
- 170 Schüz B, Wolff JK, Warner LM, *et al.* Multiple illness perceptions in older adults: effects on physical functioning and medication adherence. *Psychol Health* 2014;29:442–57.
- 171 Shi L, Zhao Y, Fonseca V, *et al.* Healthcare resource utilization, adherence and persistence with antipsychotic therapy among schizophrenia patients with vs. without pre-existing metabolic syndrome. *Curr Med Res Opin* 2010;26:2499–506.
- 172 Shin DW, Park JH, Park JH, *et al.* Antihypertensive medication adherence in cancer survivors and its affecting factors: results of a Korean population-based study. *Support Care Cancer* 2010;19:211–20.
- 173 Shoval G, Stubbs B, Balicer RD, *et al.* Low adherence to antidepressants is associated with increased mortality in Parkinson disease patients. *Parkinsonism Relat Disord* 2017;43:92–6.
- 174 Siika AM, Yiannoutsos CT, Wools-Kaloustian KK, *et al.* Active tuberculosis is associated with worse clinical outcomes in HIV-infected African patients on antiretroviral therapy. *PLoS One* 2013;8:e53022.
- 175 Slabbert FN, Harvey BH, Brink CB, *et al.* The impact of HIV/AIDS on compliance with antidepressant treatment in major depressive disorder: a prospective study in a South African private healthcare cohort. *AIDS Res Ther* 2015;12:9.
- 176 Soto A, Avila X, Cordova P, *et al.* Impact of a pharmacotherapy plan to improve adherence for patients with type-2 diabetes and hypertension in a Chilean Hospital. *Int J Clin Pharm* 2015;37:734–8.
- 177 Stack R, Bundy C, Elliott R. Intentional and unintentional non-adherence in community dwelling people with type 2 diabetes: the effect of varying numbers of medicines. *Br J Diabetes Vasc Dis* 2010;10:148–52.
- 178 Stilley CS, Bender CM, Dunbar-Jacob J, *et al.* The impact of cognitive function on medication management: three studies. *Health Psychol* 2010;29:50–5.

- 179 Stuart BC, Davidoff AJ, Erten MZ. Changes in medication management after a diagnosis of cancer among Medicare beneficiaries with diabetes. *J Oncol Pract* 2015;11:429–34.
- 180 Taira DA, Seto BK, Davis JW, et al. Examining factors associated with nonadherence and identifying providers caring for nonadherent subgroups. *J Pharm Health Serv Res* 2017;8:247–53.
- 181 Tang H-YJ, Sayers SL, Weissinger G, et al. The role of depression in medication adherence among heart failure patients. *Clin Nurs Res* 2014;23:231–44.
- 182 Thaler NS, Sayegh P, Kim MS, et al. Interactive effects of neurocognitive impairment and substance use on antiretroviral non-adherence in HIV disease. *Arch Clin Neuropsychol* 2015;30:114–21.
- 183 Vacek JL, Hunt SL, Shireman T. Hypertension medication use and adherence among adults with developmental disability. *Disabil Health J* 2013;6:297–302.
- 184 Vatcharavongvan P, Puttawanchai V. Polypharmacy, medication adherence and medication management at home in elderly patients with multiple non-communicable diseases in Thai primary care. *Fam Med Prim Care Rev* 2017;19:412–6.
- 185 Vega C, Becker RV, Mucha L, et al. Impact of adherence to antidepressants on healthcare outcomes and costs among patients with type 2 diabetes and comorbid major depressive disorder. *Curr Med Res Opin* 2017;33:1879–89.
- 186 Villar I, Izuel M, Carrizo S, et al. Medication adherence and persistence in severe obstructive sleep apnea. *Sleep* 2009;32:623–8.
- 187 Wagner GJ, Goggin K, Remien RH, et al. A closer look at depression and its relationship to HIV antiretroviral adherence. *Ann Behav Med* 2011;42:352–60.
- 188 Wakefield BJ, Holman JE, Ray A, et al. Outcomes of a home telehealth intervention for patients with diabetes and hypertension. *Telemed J E Health* 2012;18:575–9.
- 189 Warner LM, Schüz B, Aiken L, et al. Interactive effects of social support and social conflict on medication adherence in multimorbid older adults. *Soc Sci Med* 2013;87:23–30.
- 190 Wei Y-J, Simoni-Wastila L, Albrecht JS, et al. The association of antidepressant treatment with COPD maintenance medication use and adherence in a comorbid Medicare population: a longitudinal cohort study. *Int J Geriatr Psychiatry* 2018;33:e212–20.
- 191 Weiss JJ, Konstantinidis I, Boueilh A, et al. Illness perceptions, medication beliefs, and adherence to antiretrovirals and medications for comorbidities in adults with HIV infection and hypertension or chronic kidney disease. *J Acquir Immune Defic Syndr* 2016;73:403–10.
- 192 Wenze SJ, Gaudiano BA, Weinstock LM, et al. Adjunctive psychosocial intervention following hospital discharge for patients with bipolar disorder and comorbid substance use: a pilot randomized controlled trial. *Psychiatry Res* 2015;228:516–25.
- 193 Wong MCS, Liu J, Zhou S, et al. The association between multimorbidity and poor adherence with cardiovascular medications. *Int J Cardiol* 2014;177:477–82.
- 194 Wroe EB, Hedt-Gauthier BL, Franke MF, et al. Depression and patterns of self-reported adherence to antiretroviral therapy in Rwanda. *Int J STD AIDS* 2015;26:257–61.
- 195 C-H W, Balkrishnan R, Bagozzi RP. The association of race, comorbid anxiety, and antidepressant adherence among Medicaid enrollees with major depressive disorder. *Res Social Adm Pharm* 2010;8:193–205.
- 196 Wu J, Seiber E, Lacombe VA, et al. Medical utilization and costs associated with statin adherence in Medicaid enrollees with type 2 diabetes. *Ann Pharmacother* 2011;45:342–9.
- 197 Wu J-R, Lennie TA, Dekker RL, et al. Medication adherence, depressive symptoms, and cardiac event-free survival in patients with heart failure. *J Card Fail* 2013;19:317–24.
- 198 Wulaningsih W, Garmo H, Ahlgren J, et al. Determinants of non-adherence to adjuvant endocrine treatment in women with breast cancer: the role of comorbidity. *Breast Cancer Res Treat* 2018;172:167–77.
- 199 Xia Z, Xiao Z, Ma E, et al. Impact of mood disorder on medication adherence in patients with chronic diseases at a Shanghai rural hospital. *Int J Pharmacol* 2015;11:518–22.
- 200 Xue J, Conwell Y, Tang W, et al. Treatment adherence as a mediator of blood pressure control in Chinese older adults with depression. *Int J Geriatr Psychiatry* 2019;34:432–8.
- 201 Yang Y, Thumula V, Pace PF, et al. Nonadherence to angiotensin-converting enzyme inhibitors and/or angiotensin II receptor blockers among high-risk patients with diabetes in Medicare Part D programs. *J Am Pharm Assoc* 2010;50:527–31.
- 202 Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–83.
- 203 Groll DL, To T, Bombardier C, et al. The development of a comorbidity index with physical function as the outcome. *J Clin Epidemiol* 2005;58:595–602.
- 204 Bower P, Harkness E, Macdonald W, et al. Illness representations in patients with multimorbid long-term conditions: qualitative study. *Psychol Health* 2012;27:1211–26.
- 205 Bratzke LC, Muehrer RJ, Kehl KA, et al. Self-Management priority setting and decision-making in adults with multimorbidity: a narrative review of literature. *Int J Nurs Stud* 2015;52:744–55.
- 206 DiMatteo MR. Variations in patients' adherence to medical recommendations: a quantitative review of 50 years of research. *Med Care* 2004;42:200–9.
- 207 Pednekar PP, Ágh T, Malmenäs M, et al. Methods for measuring multiple medication adherence: a systematic Review-Report of the ISPOR medication adherence and persistence special interest group. *Value Health* 2019;22:139–56.
- 208 Cramer JA, Rosenheck R. Compliance with medication regimens for mental and physical disorders. *PS* 1998;49:196–201.
- 209 Piette JD, Heisler M, Ganoczy D, et al. Differential medication adherence among patients with schizophrenia and comorbid diabetes and hypertension. *Psychiatr Serv* 2007;58:207–12.
- 210 Gelenberg AJ. The prevalence and impact of depression. *J Clin Psychiatry* 2010;71:e06.
- 211 Ulley J, Harrop D, Ali A, et al. Deprescribing interventions and their impact on medication adherence in community-dwelling older adults with polypharmacy: a systematic review. *BMC Geriatr* 2019;19:15.
- 212 Dezii CM, Kawabata H, Tran M. Effects of once-daily and twice-daily dosing on adherence with prescribed glipizide oral therapy for type 2 diabetes. *South Med J* 2002;95:68–71.
- 213 Aoki T, Yamamoto Y, Ikenoue T, et al. Multimorbidity patterns in relation to polypharmacy and dosage frequency: a nationwide, cross-sectional study in a Japanese population. *Sci Rep* 2018;8:1–8.
- 214 Khan MS, Roberts MS. Challenges and innovations of drug delivery in older age. *Adv Drug Deliv Rev* 2018;135:3–38.
- 215 Gibbons CJ, Kenning C, Coventry PA, et al. Development of a multimorbidity illness perceptions scale (multiples). *PLoS One* 2013;8:e81852.
- 216 Mukhtar O, Weinman J, Jackson SHD. Intentional non-adherence to medications by older adults. *Drugs Aging* 2014;31:149–57.
- 217 Marcum ZA, Gellad WF. Medication adherence to multidrug regimens. *Clin Geriatr Med* 2012;28:287–300.
- 218 Lam WY, Fresco P. Medication adherence measures: an overview. *Biomed Res Int* 2015;2015:1–12.
- 219 Hughes CM. Medication Non-Adherence in the elderly. *Drugs Aging* 2004;21:793–811.
- 220 Stirratt MJ, Dunbar-Jacob J, Crane HM, et al. Self-Report measures of medication adherence behavior: recommendations on optimal use. *Transl Behav Med* 2015;5:470–82.
- 221 Clarke DM, Currie KC. Depression, anxiety and their relationship with chronic diseases: a review of the epidemiology, risk and treatment evidence. *Med J Aust* 2009;190:S54–60.
- 222 Read JR, Sharpe L, Modini M, et al. Multimorbidity and depression: a systematic review and meta-analysis. *J Affect Disord* 2017;221:36–46.