REVIEW

A systematic review of patient-reported measures of burden of treatment in three chronic diseases

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Background: Burden of treatment refers to the workload of health care and its impact on patient functioning and well-being. There are a number of patient-reported measures that assess burden of treatment in single diseases or in specific treatment contexts. A review of such measures could help identify content for a general measure of treatment burden that could be used with patients dealing with multiple chronic conditions. We reviewed the content and psychometric properties of patient-reported measures that assess aspects of treatment burden in three chronic diseases, ie, diabetes, chronic kidney disease, and heart failure.

Methods: We searched Ovid MEDLINE, Ovid EMBASE, Ovid PsycINFO, and EBSCO CINAHL through November 2011. Abstracts were independently reviewed by two people, with disagreements adjudicated by a third person. Retrieved articles were reviewed to confirm relevance, with patient-reported measures scrutinized to determine consistency with the definition of burden of treatment. Descriptive information and psychometric properties were extracted.

Results: A total of 5686 abstracts were identified from the database searches. After abstract review, 359 full-text articles were retrieved, of which 76 met our inclusion criteria. An additional 22 articles were identified from the references of included articles. From the 98 studies, 57 patient-reported measures of treatment burden (full measures or components within measures) were identified. Most were multi-item scales (89%) and assessed treatment burden in diabetes (82%). Only 15 measures were developed using direct patient input and had demonstrable evidence of reliability, scale structure, and multiple forms of validity; six of these demonstrated evidence of sensitivity to change. We identified 12 content domains common across measures and disease types.

Conclusion: Available measures of treatment burden in single diseases can inform derivation of a patient-centered measure of the construct in patients with multiple chronic conditions. Patients should take part in developing the measure to ensure salience and relevance.

Keywords: patient-reported outcomes, treatment burden, questionnaire, psychometric properties, self-management, patient-centered

Introduction

Burden of treatment is the workload of health care and its impact on patient functioning and well-being.[1] "Workload" consists of the demands placed on a patient by treatment for condition(s) and any associated self-care (eg, health monitoring, diet, exercise). "Impact" refers to the effect of treatment and self-care on a patient's behavioral, cognitive, physical, and psychosocial well-being. Burden of treatment is an important clinical issue because it can lead to lower rates of adherence with prescribed treatments and self-care,[2,3] and ultimately result in worse clinical outcomes, including more hospitalizations,[4] higher mortality,[4,5] and poorer health-related quality of life.[6,7] In order

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to understand better how burden of treatment can influence critical patient outcomes, robust means of measuring it must be available. Like health-related quality of life, burden of treatment is best understood from the perspective of the individual patient. Hence, it is best assessed through direct patient query.

Patients coping with multiple chronic health conditions are especially vulnerable to a sense of burden with their treatment regimen because they are often required to engage in a complex array of self-care activities in order to maintain health.[8] The number of US adults with multiple chronic health conditions is projected to rise from 57 million in 2000 to 81 million by 2020.[9] There is a paucity of available options for assessing burden of treatment in this growing patient population,[10] including no comprehensive, multidomain patient-reported measure (PRM). However, there are a number of PRMs that assess burden of treatment in single diseases or specific treatments. A review of such measures, focused specifically on identifying similarities in content across diseases and treatment, could help to determine the content for a general comprehensive measure of treatment burden, that is amenable for use across chronic diseases or with patients coping with more than one health condition.

Building a new PRM relies on triangulation of multiple and diverse methods, often used in a stepwise fashion.[11–14] The first steps usually involve direct patient query of the phenomena of interest and a literature review of existing instruments in related areas.[11,14] We outlined a preliminary measurement framework of treatment burden in a recent study.[1] The framework was derived from 32 semistructured interviews with patients, all with complex self-care regimens (including polypharmacy) and most coping with multiple chronic health conditions. The framework is currently undergoing further qualitative testing in a new sample of socioeconomically disadvantaged patients. Currently, there are no systematic reviews of PRMs of treatment burden. The review of PRMs described in this report is designed to augment and verify the developing measurement framework, while also informing item content for a new comprehensive measure of treatment burden.

We searched the available scientific literature for PRMs of treatment burden in three disease types, ie, diabetes, chronic kidney disease, and heart failure. These three chronic diseases were selected because they all can involve rather complicated long-term management plans requiring considerable time, effort, and financial investment from patients,[6,15,16] and because of their interrelationship with one another, including the fact that diagnosis of one can raise

the risk of diagnosis of the others.[17] The PRMs identified contain components consistent with our above definition of treatment burden and could include full scales, scales within measures, or other scorable components, like single items. The systematic review has three objectives. First, to identify PRMs of treatment burden in diabetes, chronic kidney disease, and heart failure, including full measures, scales within measures, or other scorable components within measures; second, to identify common content domains of treatment burden, given that common domains that cut across measures and disease types can help inform the content of a general measure of treatment burden; and third, to summarize measure characteristics and psychometric properties, eg, reliability, scaling structure, validity, and sensitivity to change. While documentation of these performance characteristics could help investigators to select an appropriate measure of treatment burden for use in the diseases targeted, the primary aim of this summary is to identify psychometrically sound measures, scales, and items that can inform the content of a general (not disease-specific) measure of burden.

Materials and methods
Database search and abstract review
We searched Ovid MEDLINE, Ovid EMBASE, Ovid PsycINFO, and EBSCO CINAHL (Cumulative Index to Nursing and Allied Health Literature) through November 2011. An information specialist (PJE) created and ran the search strategies. Sample terms used in the searches included "self-care", "workload", "burden", and "lifestyle" crossed with "questionnaire", "scale", "measure", and "survey" and the three targeted diseases, diabetes (types 1 and 2), chronic kidney disease, and heart failure. Full search strategies for each database are accessible at http://mayoresearch.mayo.edu/mayo/research/hsr/burden-of-treatment.cfm.

Abstracts were downloaded into a reference software library (Endnote X4®), then uploaded to a web-based systematic review software program (DistillerSR) where they were reviewed. All abstracts were double-reviewed for relevance and fit with the inclusion criterion of an article reflecting original research describing the development, validation, or use of a PRM of treatment burden in diabetes, chronic kidney disease, or heart failure. To assist reviewers in selecting appropriate measures, a working definition was provided on the abstraction form ("the burden of treatment is the negative impact of treatment and care on a patient's daily routine through the investment of time, money, and effort into health care"). Disagreements between abstract reviewers were adjudicated by either DTE or KJY, given

their expertise with PRMs and familiarity with the burden of treatment construct that was discussed by these two authors prior to and during adjudication.

Article retrieval, determination of inclusion, and data extraction

Full-text articles of relevant abstracts were retrieved, uploaded to DistillerSR, and screened for relevance by DTE and KJY. Together, these authors carefully scrutinized each article, reviewing the items on each PRM (as included in the article or as identified through additional search for the actual measure), and determining which aspects of each measure were consistent with the working definition of treatment burden. This step was critical because in many instances an entire measure was not relevant, but portions of it were (eg, subscales). The components of each measure consistent with our definition of treatment burden were eligible for data extraction. A component (ie, full measure or subscale within a measure) was included for extraction if at least half of its items reflected treatment burden. Reference sections of the included articles were a secondary source of relevant articles missed by the database searches.

Any English language article describing the development or use of a PRM of treatment burden (as defined above) in one of the targeted diseases was included for data extraction. Articles were excluded if they: did not develop, validate, or use a PRM of treatment burden; did not provide any psychometric characteristics of the measure; described a product or device-specific patient preference or satisfaction measure; employed questionable methods (eg, very small sample sizes); or did not describe an original research study. For each article, data extractors were provided with the name of the measure as well as the component(s) of the measure that reflected treatment burden. They were instructed to extract descriptive information about the study (eg, sample size, age and gender of participants, disease focus) and psychometric data on the measure. When available, the following psychometric information were extracted for each measure: whether direct patient input was used during development; reliability, specifically internal consistency and test-retest; scale analysis, specifically factor analysis and item-total correlations; convergent and discriminant validity, ie, convergence with conceptually similar measures and divergence with conceptually dissimilar measures; known-groups validity or the ability of the PRM to differentiate known patient groups; concurrent validity or correlation of the PRM with meaningful clinical characteristics; and sensitivity to change or the ability of the PRM to reflect underlying change in patient status over time.

Data extractors (JLR, AJ, JSE) were trained by DTE. Prior to beginning the task, each extractor completed two sample extractions, with their results checked and didactic feedback provided by DTE, who also provided continued scientific support throughout the process. The extraction form was created by RJM, and TAE maintained the DistillerSR database, managed the extraction process including reviewer assignments, and provided technical support. All data extractions were checked for accuracy by one of the PRM experts (DTE or KJY).

Results
Study screening and inclusion

Figure 1 shows the process by which studies were screened and selected for inclusion. The database search yielded 5686 articles, of which 359 were retrieved for full-text review. After review of the full texts, 283 articles were excluded from further consideration, mostly because they did not develop, validate, or use a PRM of treatment burden. Several retained articles referenced other studies of possible relevance. Twenty-two of these were retrieved and deemed eligible for data extraction. Hence, a total of 98 articles were targeted for data extraction.

Identified measures of treatment burden

Fifty-seven PRMs of treatment burden were identified in the 98 articles selected for inclusion (see Table 1 for a list of the measures). Most (47, 82%) assessed treatment burden in diabetes, but six (11%) assessed treatment burden in kidney disease and four (7%) in heart failure. Based on their focus and contents, we categorized the measures into one of the following eight types: treatment/regimen-related impact and burden, barriers to self-care, distress, insulin treatment, family conflict/strain, general diabetes quality of life, glucose monitoring, or treatment satisfaction. Most of the measures represented in Table 1 (51, 89%) are scored as multi-item scales (ie, multiple items are combined to form a single score). The rest (6, 11%) score responses to only single items. This includes measures made up of only a single, standalone item[18–20] as well as measures made up of multiple items that report scores for only individual items (eg, Survey of Treatment Burdens in Diabetes,[2,21] Perceived Difficulties in Diabetes Self-Care,[22] and Perceptions of Insulin Shots and Fingersticks[23]). Finally, some measures (12, 21%, all in diabetes) are suitable for administration in children or adolescents, including a few that are specifically tailored to this population (eg, the DISABKIDS Diabetes module[24] and the Pediatric Quality of Life Inventory 3.0 Diabetes module[25]).

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│ Potentially eligible studies     │
│ identified through database      │
│ searches (5686)                  │
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              │                       │ Excluded after abstract screening │
              ▼                       │ (5327)                            │
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│ Articles selected for full-text  │
│ retrieval (359)                  │
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              │──────────────────────►┌──────────────────────────────────────────┐
              │                       │ Excluded after full-text screening (283)   │
              │                       │ ▪ Does not develop, validate or test        │
              │                       │   patient-reported measure of treatment     │
              │                       │   burden (234)                               │
              ▼                       │ ▪ Investigator-generated measure with no     │
┌─────────────────────────────────┐  │   psychometrics provided (27)                │
│ Articles from database searches  │  │ ▪ Questionable methods used (12)             │
│ identified for full extraction   │  │ ▪ Other reasons (6)                          │
│ (76)                             │  │ ▪ Product-specific patient preference or     │
└─────────────────────────────────┘  │   satisfaction survey (2)                    │
              │                       │ ▪ Not original research (2)                  │
              │                       └──────────────────────────────────────────┘
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│ Additional articles identified   │──►
│ from references for full         │
│ extraction (22)                  │
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│ Studies fulfilling inclusion     │
│ criteria and included in         │
│ analysis (98)                    │
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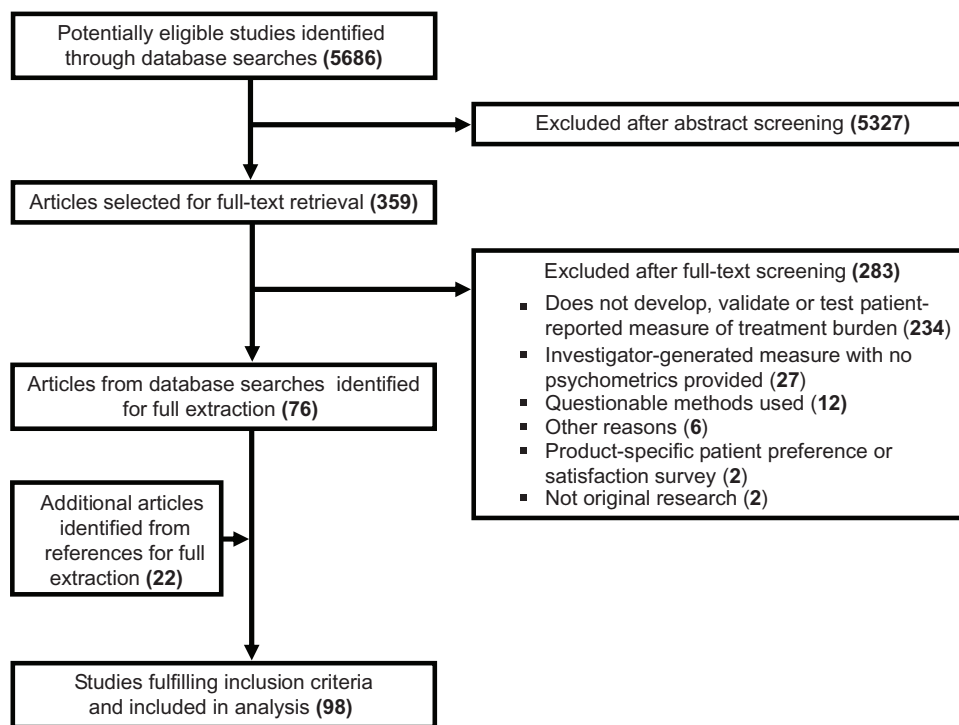
Figure 1 Flow diagram of study screening and selection.

Common content domains of treatment burden

Table 2 provides a summary of all measures including a description of the contents of each measure and a summary of key psychometric properties. The instrument name and specific subscales relevant to treatment burden (or scorable components in the case of single items) appear in the first two columns of the table. This information, along with a review of item wording of each relevant measure, provides a general sense of the common content domains reflected in the measures. We identified the following 12 content domains as common to two or more of the identified measures: emotional impact/regimen-related distress,[6,23,24,26–38] family conflict/unsupportive behavior from others,[39–44] convenience of treatment (eg, insulin, oral medications),[2,6,19,21,22,24,25,29,38,45–57] self-care convenience (eg, exercise, foot care, overall impression of self-care),[22,24,25,37,38,48,51,56–60] monitoring burden (eg, glucose monitoring),[2,21,22,24,25,38,49,53,56–58,60–63] lifestyle impact (including social restrictions and work interference),[2,6,21,24,33,36,37,46,47,50,52,58,62,64,65] scheduling flexibility,[26,29,46,47] medication side effects,[29,46,47,55] diet/food-related problems,[2,21,22,25,32,38,48,49,53,55–57,60,66] overall treatment burden,[18,67] device function/bother (eg, insulin delivery device, kidney dialysis),[6,34,35,52] and economic burden.[20,51,59,68] Several measures assess multiple content domains. For example, the DISABKIDS Diabetes module and the Personal

Diabetes Questionnaire each assess five content domains. Eight other measures assess four content domains (Barriers to Adherence Questionnaire, Diabetes Medication Satisfaction Measure, Diabetes Medication Treatment Satisfaction Tool, General Barriers to Diabetes Self-Management, PedsQL 3.0 Diabetes module, Perceived Difficulties in Diabetes Self-Care, Perceptions About Medications for Diabetes, and the Survey of Treatment Burdens in Diabetes).

Psychometric properties of treatment burden measures

The 98 studies included in this review provided a considerable amount of scale and psychometric data on the identified measures. Detailed tables featuring all extracted data are accessible at http://mayoresearch.mayo.edu/mayo/research/hsr/burden-of-treatment.cfm. Table 2 provides a summary of the extracted data for each measure. Measurement properties featured in the table include patient input, reliability (internal consistency and test-retest), scale analysis (factor analysis, item-total correlation), convergent and discriminant validity, known-groups/concurrent validity, and sensitivity to change. Consistency of each property with a minimum standard of acceptability is indicated in the table.

Patient input

Directly incorporating patient views during item generation is now considered standard practice when developing a patient-centered,

Table 1 Identified patient-reported measures assessing burden of treatment (57)

Diabetes measures (47)

Treatment/regimen-related impact and burden measures (8)
Diabetic Foot Ulcer Scale
Multidimensional Diabetes Self-Management Checklist
Perceived Burden of Diabetes Treatment (single item)
Perceptions About Medications for Diabetes
Practicality/comfort of treatment (single item)
Survey of Treatment Burdens in Diabetes (individual item scoring)
Treatment-Related Impact Measure – diabetes
Treatment-Related Impact Measure – diabetes device

Barriers to self-care measures (8)
Barriers in Diabetes Questionnaire
Barriers to Adherence Questionnaire
Barriers to Diabetes Adherence[child]
Diabetes Self-Care Barriers Assessment for Older Adults
Dietary Barriers
General Barriers to Diabetes Self-Management
Perceived Difficulties in Diabetes Self-Care (individual item scoring)
Personal Diabetes Questionnaire

Distress measures (7)
Diabetes Distress Scale (including 2-item, 3-item, and 4-item short versions)
Diabetes Fear of Injecting and Self-testing Questionnaire[child]
Perceptions of Insulin Shots and Fingersticks (individual item scoring)[child]
Problem Areas in Diabetes

Insulin treatment measures (6)
Insulin Delivery System Rating Questionnaire
Insulin Pen Questionnaire
Insulin Treatment Appraisal Scale
Insulin Treatment Questionnaire
Insulin Treatment Satisfaction Questionnaire
Patient Satisfaction with Insulin Therapy

Family conflict/strain measures (6)
Diabetes Family Adherence Measure[child]
Diabetes Family Behavior Checklist[child]
Diabetes Family Conflict Scale[child]
Diabetes Family Support and Conflict Scale
Diabetes Responsibility and Conflict Scale[child]
Multidimensional Diabetes Questionnaire

General diabetes quality-of-life measures (5)
Diabetes-39
Diabetes Health Profile
Diabetes-specific Quality of Life Scale
DISABKIDS Diabetes module[child]
Pediatric Quality of Life Inventory 3.0 Diabetes module[child]

Glucose monitoring measures (4)
Blood Glucose Monitoring System Rating Questionnaire
Continuous Glucose Monitoring Satisfaction Scale[child]
Glucose Monitoring Survey[child]
Measure of Invasiveness as a Reason for Skipping Self-Monitoring of Glucose

Treatment satisfaction measures (3)
Diabetes Medication Satisfaction Measure
Diabetes Medication Treatment Satisfaction Tool
Treatment Satisfaction Measure for People with Insulin-dependent Diabetes[child]

(*Continued*)

Table 1 (*Continued*)

Kidney disease measures (6)

Treatment/regimen-related impact and burden measures (2)
Renal Adherence Attitudes Questionnaire
Treatment Effects Questionnaire

Distress measures (2)
Continuous Ambulatory Peritoneal Dialysis Stressor Scale
Hemodialysis Stressor Scale

Barriers to self-care measures (1)
Health Beliefs about Fluid Adherence

Treatment satisfaction measures (1)
Satisfaction with Care Questionnaire

Heart failure measures (4)

Barriers to self-care measures (3)
Beliefs about Dietary Compliance Scale
Beliefs about Medication Compliance Scale
Dietary Sodium Restriction Questionnaire

Treatment/regimen-related impact and burden measures (1)
Perceived difficulty affording health care (single item)

Note: [child]suitable for administration to children and adolescents.

self-report measure.[11] This is typically done using qualitative methods, such as individual interviews or focus groups; however, patient surveys are sometimes used as well. More than half of the measures (38, 67%) showed evidence of being developed from direct patient input via individual interviews, focus groups, surveys, or combinations of these methods (Table 2).

Reliability

Internal consistency (Cronbach's alpha) and test-retest (Pearson r or intraclass correlation) were frequently reported measures of reliability. The standard threshold for acceptable reliability of measures used for group comparison is 0.70.[69] Most of the measures (46, 81%) demonstrated acceptable reliability, usually internal consistency (Table 2). Nine measures also demonstrated acceptable test-retest reliability, including the Diabetes Family Adherence Measure, Glucose Monitoring Survey, Insulin Treatment Satisfaction Questionnaire, Perceptions about Medications for Diabetes, Problem Areas in Diabetes, Treatment-Related Impact Measure-Diabetes, Treatment-Related Impact Measure-Diabetes Device, Hemodialysis Stressor Scale, and Renal Adherence Attitudes Questionnaire. Retest magnitudes may have been attenuated in certain measures due to long retest intervals. For example, retest intervals for the Barriers to Adherence and Diabetes Family Behavior Checklist were reported as six months,[40,56] a span of time in which patient status could have changed. Reliability was unavailable for all measures scoring single items.

Scale analysis

Content domains apparent in multi-item scales can be verified using factor analysis and item-total scale correlations.

Table 2 Summary of scale characteristics and psychometric properties

Instrument	Relevant subscales, items (n)	Patient input	Reliability	Scale analyses	Convergent/ discriminant validity	Known-group/ concurrent validity	Sensitive to change
Diabetes measures							
Barriers to Adherence Questionnaire[56,92]	Diet (4), insulin injection (3), exercise (3), glucose testing (5), total (15)	✓	X	NR	NR	✓	NR
Barriers to Diabetes Adherence[26]	Stress/burnout (4), time pressure/ planning (5), stigma (6)	✓	✓	✓	NR	✓	NR
Barriers in Diabetes Questionnaire[49]	Self-control and advice from providers (9), injecting, monitoring and overall self-regulation (10), self-regulation in specific situations (9), total (28)	X	✓	✓	NR	✓	NR
Blood Glucose Monitoring System Rating Questionnaire[58,93]	Convenience (NR), interference (NR), blood glucose burden (NR)	X	✓	NR	NR	✓	X
Continuous Glucose Monitoring Satisfaction Scale[61,62,78]	Hassles (20)	X	✓	✓	NR	✓	NR
Diabetes-39[67,94]	Diabetes control (12)	✓	✓	✓	✓	✓	NR
Diabetes Distress Scale[28,73,84,95]	Emotional burden (5), regimen-related distress (5)	✓	✓	✓	✓	✓	✓
DDS-2, DDS-3, and DDS-4[27]	Totals for scales (2-items, 3-items, and 4-items, respectively)	✓	✓	NR	✓	✓	✓
Diabetes Family Adherence Measure[39]	Coercion (7)	X	✓	✓	✓	✓	NR
Diabetes Family Behavior Checklist[40,96]	Nonsupportive behaviors (7)	✓	X	NR	✓	✓	✓
Diabetes Family Conflict Scale-Revised[41,86,97–100]	Direct management (9), indirect management (10), total (19)	✓	✓	✓	✓	✓	✓
Diabetes Family Support and Conflict Scale[42]	Family conflict (4)	✓	✓	✓	NR	✓	NR
Diabetes Fear of Injecting and Self-testing Questionnaire[30,79,91]	Self-injecting fear (15), self-testing fear (15), total (30)[a]	X	✓	✓	✓	✓	NR
Diabetes Health Profile[37,82,101,102]	Barriers to activity (NR)	✓	✓	✓	✓	✓	✓
Diabetes Medication Satisfaction Measure[46,81,90,103]	Burden (11), symptoms (5)	✓	✓	✓	✓	✓	✓
Diabetes Medication Treatment Satisfaction Tool[47]	Lifestyle (5), convenience (3), well-being (3)	✓	✓	✓	NR	✓	NR
Diabetes-specific Quality of Life Scale[48,75,80]	Diet restrictions (9), daily hassles (6)	✓	✓	✓	✓	✓	✓
Diabetes Responsibility and Conflict Scale[43]	Conflict (NR)	X	NR	NR	NR	X	NR
Diabetes Self-Care Barriers Assessment for Older Adults[60,104]	Glucose monitoring barriers (4), diet regimen barriers (4), exercise barriers (4), total (12)	✓	✓	✓	NR	✓	NR
Diabetic Foot Ulcer Scale[59,105]	Ulcer care (4), financial (2)	✓	✓	✓	✓	✓	X
DISABKIDS Diabetes module[24,106]	Impact/acceptance (6), treatment (4)	✓	✓	✓	NR	✓	NR
General Barriers to Diabetes Self-Management[57,107]	Diet (7), exercise (7), glucose testing (7), medication taking (7), general barriers (4), total (31)	✓	✓	NR	NR	✓	NR
Dietary Barriers[57,107]	At home (7), food purchase (8), away from home (5), total (27)	✓	✓	NR	NR	✓	NR
Glucose Monitoring Survey[62]	Glucose control (7), social complications (6), total (22) (note, 9 items do not load on either subscale)	X	✓	✓	✓	✓	NR

Measure	Subscales (items)						
Insulin Delivery System Rating Questionnaire[50,58,93]	Convenience (NR), interference (NR), blood glucose burden (NR)[b]	✓	✓	NR	NR	✓	✓
Insulin Pen Questionnaire[51]	Convenience (7), facilitation of self-care (6), cost (1)	✓	✓	NR	✓	NR	✓
Insulin Treatment Appraisal Scale[31]	Negative appraisal (16)	✓	✓	✓	✓	✓	✓
Insulin Treatment Questionnaire[45]	Insulin therapy perception (12)	X	X	✓	X	X	X
Insulin Treatment Satisfaction Questionnaire[52,108–111]	Inconvenience of regimen (5) lifestyle flexibility (3), delivery device satisfaction (6)[c]	✓	✓	✓	✓	✓	X
Measure of Invasiveness as a Reason for Skipping Self-Monitoring of Glucose[63]	Total (7)	X	✓	NR	✓	✓	
Multidimensional Diabetes Questionnaire[44]	Misguided support behaviors (4)	✓	✓	✓	✓	NR	NR
Multidimensional Diabetes Self-Management Checklist[53]	Burden of diet self-management (3), burden of injecting insulin (3), burden of glucose monitoring (3), burden of adjusting insulin dose (3)	X	✓	NR	NR	NR	NR
Patient Satisfaction with Insulin Therapy[54,74]	Convenience/ease (10), social comfort (5), global satisfaction (15)	✓	✓	✓	NR	NR	✓
Pediatric Quality of Life Inventory 3.0 Diabetes module[25,112,113]	Treatment barriers (4), treatment adherence (7)	✓	X	✓	✓	✓	NR
Perceived Burden of Diabetes Treatment[18]	Single item on perceived burden of treatment	X	NR	NA	NR	NR	NR
Perceived Difficulties in Diabetes Self-Care[22]	Individual items assessing difficulties in insulin treatment (2), glucose monitoring (1), diet (3), exercise (1), smoking (1), daily self-care (1), and self-care during certain occasions (4)	✓	NR	NR	NR	✓	NR
Perceptions About Medications for Diabetes[29]	Schedule flexibility (3), portability convenience (2), regimen inconvenience (5), difficulty remembering medications (2), gastrointestinal side effects (3), weight/edema side effects (3), emotional (10)	✓	✓	✓	✓	✓	NR
Perceptions of Insulin Shots and Fingersticks[23]	Injection pain (1), injection fear (1), fingerstick pain (1), fingerstick fear (1)	X	NR	NR	NR	✓	X
Personal Diabetes Questionnaire[38]	Diet barriers (7), medication barriers (8), monitoring barriers (8), exercise barriers (7)	✓	✓	NR	NR	✓	NR
Practicality/comfort of treatment[19]	Single item on practicality and comfort of treatment	X	NR	NA	NR	NR	NR
Problem Areas in Diabetes[32,77,83,114]	Treatment-related (3) and food-related problems (3)	✓	✓	✓	✓	✓	✓
Survey of Treatment Burdens in Diabetes[2,21]	Individual items assessing burden of: oral agents (1), insulin (4), oral + insulin therapy (1), self-monitoring of blood glucose (3), diet (2), pain (1), and interference with activities (1)	X	NR	NR	NR	✓	NR
Treatment-Related Impact Measure – Diabetes[6]	Treatment burden (6), daily life (5), psychological health (8)	✓	✓	✓	✓	✓	NR
TRIM-Diabetes Device[6]	Device function (5), bother (3), total (8)	✓	✓	✓	✓	✓	NR
Treatment Satisfaction Measure for People with Insulin-dependent Diabetes[64]	Perceived compatibility with lifestyle (PCL) (3)	✓	NR	NR	NR	✓	NR

(Continued)

Table 2 (Continued)

Instrument	Relevant subscales, items (n)	Patient input	Reliability	Scale analyses	Convergent/ discriminant validity	Known-group/ concurrent validity	Sensitive to change
Kidney disease measures							
Health Beliefs About Fluid Adherence[33]	Barriers to fluid adherence (7)	X	√	NR	NR	√	NR
Hemodialysis Stressor Scale[34,35,85,115]	Physiological, psychosocial, total[d]	X	√	√	NR	X	√
Continuous Ambulatory Peritoneal Dialysis Stressor Scale[35]		X	√	NR	NR	NR	NR
Renal Adherence Attitudes Questionnaire[65]	Attitude towards social restrictions (8), acceptance/lifestyle impact (11)	√	√	√	NR	NR	NR
Satisfaction with Care Questionnaire[68]	Financial/transportation (7)	√	√	NR	√	NR	NR
Treatment Effects Questionnaire[16,36,76]	Total (20)	X	√	NR	√	√	NR
Heart failure measures							
Beliefs about Medicine Compliance Scale[55,116]	Medication barriers (6)	√	√	√	NR	NR	NR
Beliefs about Diet Compliance Scale[55,116,117]	Diet barriers (5)	√	√	√	NR	X	NR
Dietary Sodium Restriction Questionnaire[66,118]	Perceived behavioral control (7)[e]	√	√	√	NR	NR	NR
Perceived Difficulty Affording Health Care[20,72]	Single item on economic burden of medical costs	X	NR	NA	NR	√	NR

Notes: [a]Mollema et al[30] added 4 items to fear of injecting and 4 items to fear of self-testing subscales; ie, treatment satisfaction (15 items) and treatment interference with activities (11 items); [b]modified from original scoring[50] which scored two subscales; [c]Bode et al[108] used a modified scoring procedure for all subscales; [d]number of items in the subscales and the overall scale fluctuate across studies. A third subscale ("dependency/restriction") was identified by Murphy et al;[115] [e]original scoring[118] recorded only response frequencies of individual items.
Abbreviations: √, satisfactory; X, unsatisfactory or incomplete; NR, not reported; NA, not applicable.

Exploratory factor analytic techniques like principal components analysis and/or confirmatory factor analysis were used in a number of studies, and supported the treatment burden domains identified in most measures (32, 56%). Exploratory factor analyses typically support content domains through reporting of variance explained; confirmatory factor analysis supports content domains through report of goodness of fit indices. Fifteen of these measures also demonstrated adequate item-total scale correlations (ie, Barriers to Diabetes Adherence, Diabetes-39, Diabetes Family Support and Conflict Scale, Diabetes Fear of Injecting and Self-testing Questionnaire, Diabetes Health Profile, Diabetes-specific Quality of Life Scale, Diabetic Foot Ulcer Scale, Insulin Treatment Appraisal Scale, Insulin Treatment Satisfaction Questionnaire, Patient Satisfaction with Insulin Therapy, Perceptions About Medications for Diabetes, Hemodialysis Stressor Scale, Beliefs about Medicine Compliance Scale, Beliefs about Diet Compliance Scale, and Dietary Sodium Restriction Questionnaire). An adequate item-total scale correlation is >0.20.[14]

Convergent and discriminant validity

Convergent validity was determined by the degree of convergence (ie, correlation) of the treatment burden measure with other conceptually similar measures; discriminant validity was determined by the degree of divergence (ie, lack of correlation or low correlation) with other conceptually dissimilar measures. A medium-sized correlation ($r \geq 0.30$)[70] may be used to support convergent validity. Discriminant validity is supported by a pattern of low correlations with measures and indicators that are unrelated to the target measure.[14] As shown in Table 2, less than half of the measures (23, 40%) demonstrated evidence of convergent or discriminant validity. In most instances, convergent validity alone was supported. For example, in validating the Insulin Treatment Appraisal Scale, Snoek et al found negative insulin appraisal scores were associated with more total diabetes distress on the Problem Areas in Diabetes questionnaire ($r = 0.33$).[31] Among patients with end-stage renal disease, Griva et al found that the total treatment disruptiveness score of the Treatment Effects Questionnaire was strongly associated with the total illness disruptiveness score of the Illness Effects Questionnaire ($r = 0.83$).[36] Only four measures showed any evidence of discriminant validity (Diabetes Family Adherence Measure, Insulin Treatment Satisfaction Questionnaire, Problem Areas in Diabetes, and Treatment Effects Questionnaire).[32,36,39,52] For example, while the coercion scale of the Diabetes Family Adherence Measure has been found to be highly associated

with the nonsupportive behaviors scale of the Diabetes Family Behavior Checklist (r = 0.65), it is much less associated with the warmth/caring (r = 0.22) and guidance/control (r = 0.14) subscales of the Diabetes Family Behavior Scale.[39] Evidence of convergent and discriminant validity was absent for measures scoring single items.

Known-groups and concurrent validity

Clinical utility of the measures was observed in the following ways: by noting differences in scores across meaningful groups of patients (ie, known-groups validity), and by noting correlations of scores with meaningful clinical, health status, or sociodemographic indicators (ie, concurrent validity). Known-groups validity was considered supported if clinically differentiable patient groups differed significantly on the measure in expected ways.[71] Concurrent validity was evidenced by a statistically significant correlation of at least a moderate magnitude, or in this case ≥ 0.20.[70] As Table 2 shows, most of the measures (47, 82%) demonstrated evidence of known-groups and/or concurrent validity. This included five of the six measures scoring single items.[2,18,20,22,23,72] Sample patient groupings on which measure scores significantly differed include continuous glucose monitoring (users versus nonusers),[62,73] insulin use (yes versus no, type of insulin),[31,74,75] dialysis type,[76] insurance status,[57] and mental health status.[6,77] Clinical indicators such as hemoglobin A1c and adherence with self-care were consistently associated with measure scores across numerous studies, with greater treatment burden associated with higher hemoglobin A1c[6,25,27,38,39,41,49,54] and poorer adherence with self-care.[2,26,28,40,56,63,64] Other variables frequently associated with measure scores included age (younger age, more burden)[6,28,78,79] and self-reported health (poorer health, more burden).[49,67,79]

Sensitivity to change

The ability of the treatment burden measure to detect any change in patient status over time (ie, sensitivity to change)[14] was noted in a few measures (11, 19%, Table 2). A commonly observed result was a statistically significant decline in treatment burden after a successful medical or psycho-educational intervention.[45,58,80–86] In only three studies was a standard index of sensitivity also calculated, specifically, Cohen's effect size.[45,81,85]

Patient-centered measures with evidence of reliability and validity

Of the 57 measures of treatment burden identified in this analysis, 15 (26%) were developed with direct patient input and had demonstrable evidence of reliability and multiple forms of validity. This included the following measures: Diabetes-39, Diabetes Distress Scale (including the 2-item, 3-item, and 4-item short versions), Diabetes Family Conflict Scale, Diabetes Health Profile, Diabetes Medication Satisfaction Measure, Diabetes-specific Quality of Life Scale, Diabetic Foot Ulcer Scale, Insulin Treatment Appraisal Scale, Insulin Treatment Satisfaction Questionnaire, Problem Areas in Diabetes, Treatment-Related Impact Measure-Diabetes, and Treatment-Related Impact Measure-Diabetes Device. Six of these measures also demonstrated evidence of sensitivity to change (Diabetes Distress Scale, Diabetes Family Conflict Scale, Diabetes Health Profile, Diabetes Medication Satisfaction Measure, Diabetes-specific Quality of Life Scale, and Problem Areas in Diabetes).

Discussion

To our knowledge, this is the first systematic review of PRMs for burden of treatment. In this review, we identified 57 measures across three chronic conditions, ie, diabetes, kidney disease, and heart failure. There appear to be a number of adequate PRMs tapping various aspects of treatment and self-care burden, mainly in diabetes. Possible explanations for the imbalance in representation favoring diabetes include the self-management complexity of this disease, the fact that diabetes impacts both children and adults, and the speed with which new treatments and management technologies become available for this disease. Indeed, 40% of the diabetes studies reviewed received funding support from a pharmaceutical or device manufacturer, compared with only 18% for kidney disease and heart failure studies combined. While our intent in this analysis was not to evaluate the sufficiency of treatment burden measurement in the three targeted conditions, the results appear to support the need for development of more measures in kidney disease and heart failure. No single kidney disease or heart failure measure satisfied all of the psychometric criteria reviewed. Most of the measures reviewed (89%) are scored as multi-item scales in which multiple items are aggregated to form a score. Measures scoring responses to single items tended to have poorer psychometric properties, with reliability infrequently reported. Also, the availability of measures suitable for administration in children (specifically diabetes) signals the relevance of treatment burden beyond adults.

Several common content domains emerged that cut across the measures and disease types, supporting conceptualization of a general burden of treatment construct. Table 3 shows the 12 content domains that were represented in two or more PRMs. Seven of these domains (emotional impact or regimen-related distress, treatment convenience, lifestyle impact,

Table 3 Content domains common across burden of treatment measures

Emotional impact/regimen-related distress	Scheduling flexibility
Family conflict/unsupportive behavior	Medication side effects
Treatment convenience	Diet/food-related problems
Self-care convenience	Overall treatment burden
Monitoring burden	Device function/bother
Lifestyle impact (includes social restrictions and work interference)	Economic burden

medication side effects, diet or food-related problems, device function or bother, and economic burden) were represented in PRMs from at least two of the targeted diseases. Economic burden was represented in PRMs of all three diseases. The heterogeneity of the content domains that emerge from these measures lends support to a multidimensional conceptualization of treatment burden, a quality supported by other recent research on the construct,[87–89] including our own formative qualitative work.[1]

Identifying PRMs of treatment burden required identifying measures of a wide number of related constructs like "barriers to self-care", "distress", "treatment impact", "treatment satisfaction", and "quality of life". Measures of these constructs, many of which are multidimensional, contain elements reflective of treatment burden as well as other concepts. Hence, we needed to examine carefully the components of each measure, including the contents of subscales and even individual items. For example, the Treatment-Related Impact Measure-Diabetes, a measure of treatment impact, contains five subscales, three of which reflect treatment burden (treatment burden, daily life, and psychological health) and two of which do not (management beliefs and compliance). The Diabetes-39, a measure of diabetes-specific quality of life, also consists of five subscales, but only the 12-item control subscale specifically addresses the degree to which treatment and self-care affect quality of life. The other four subscales do not differentiate burden due to the illness from burden due to treatment or self-care. However, there were some instances in which entire measures were judged consistent with the construct of treatment burden (eg, the Diabetes Family Conflict Scale and the Hemodialysis Stressor Scale).

Standard psychometric performance criteria were used to evaluate the quality of each of the identified PRMs. While a review of performance characteristics could help select a measure of treatment burden for use in one of the three diseases targeted, our principal aim was to identify psychometrically sound scales and items that could inform item content for a general non-disease-specific measure. Our review identified 15 measures with acceptable psychometric characteristics in most of the categories extracted including direct patient input, reliability, scaling structure (ie, factor analysis), convergent and/or discriminant validity, and known-groups and concurrent validity. Six of these 15 measures were also sensitive to changes in patient health status over time (the Diabetes Distress Scale, Diabetes Family Conflict Scale, Diabetes Health Profile, Diabetes Medication Satisfaction Measure, Diabetes-specific Quality of Life Scale, and Problem Areas in Diabetes). Authors of a few measures did stipulate clinically meaningful score differences or threshold cut points for serious problems.[6,23,90,91] There was no evidence of use of more modern psychometric approaches such as item response theory. This is a notable absence given that item response theory-based metrics like item-information and scale-information function and analyses like differential item functioning can provide critical psychometric data that classical test theory methods cannot.

Methodological challenges

There were several challenges associated with conducting this systematic review. Given that most conceptualizations of treatment burden are of relatively recent origin, developing a literature search strategy that is both sensitive and specific proved difficult. Gallacher et al reported the same challenge in a review of qualitative literature.[87] Inherent limitations in the way in which articles are currently indexed required that we develop and run a rather broad, highly sensitive but nonspecific, database search strategy. Consequently, our searches identified a large number of articles, most of which failed to meet inclusion criteria for the review. Of the total number of abstracts identified (5686), only 6% (359) were deemed relevant enough to warrant article retrieval. Of these, only 76 articles (21%) fulfilled the inclusion criteria and were extracted, or slightly over 1% of the total number of abstracts identified by the searches. Further, our belief that the burden of treatment is a multidimensional construct also contributed to the expansive nature of the search strategy. Since we expected some variability in the content domains represented in the different measures, the searches consisted of a number of expanded Boolean searches using the "or" connector rather than more limited searches using "and". The nonspecificity of the searches was also compounded by the number of terms synonymous with "patient-reported measure", including "measure", "questionnaire", "instrument", "tool", "scale", and "survey". Finally, during examination of full-text articles, it became apparent that most measures were not designed to assess treatment burden exclusively; hence, it took considerable effort to scrutinize and tease out

those specific components of each measure that addressed the construct as we defined it.

Limitations

Our review does have a few limitations. The concept of a general burden of treatment is relatively novel, although we have shown that a number of previously developed PRMs do assess components of it within individual disease contexts. Given that the current state of the science is actively evolving, there is bound to be some disagreement about what does and what does not constitute treatment burden. We attempted to identify domains and PRMs consistent with our own definition of the construct.[1] It is possible that a different conceptualization could result in identification of a slightly different set of domains and measures. Second, in order to make for a manageable review, we needed to limit the number of chronic conditions. It is possible that a different set of targeted conditions might reveal other content domains not represented in this review. However, we are encouraged by the findings of a recently published concept analysis of the treatment burden literature in six major chronic illnesses that confirms many of the same domains uncovered in our review of measures, including emotional impact, treatment and self-care convenience, lifestyle impact, scheduling flexibility, medication side effects, device function/bother, and economic burden.[89] Third, study heterogeneity in both methods and the reporting of results precluded use of a more formal quantitative pooling technique such as meta-analysis. Fourth, only English language studies were selected for extraction; hence, we may have missed a few relevant measures unavailable in English. Finally, while all abstracts were reviewed by two people and disagreements were adjudicated by a third reviewer, it is possible that a relevant article was inadvertently excluded by the two abstract reviewers.

Conclusion

This systematic review of PRMs is a companion piece to our earlier qualitative study that articulated a patient-informed conceptual framework of the burden of treatment.[1] Most of the content domains identified in this review coincide with themes and subthemes articulated in the framework. Three domains, ie, emotional impact, diet or food-related problems, and device function or bother, are currently not represented in the framework. However, we are continuing to refine this conceptual framework with additional qualitative data from interviews with socioeconomically disadvantaged patients. The ultimate result of all these efforts will be a measurement framework that will provide the foundation on which a patient-centered measure of treatment burden will be built.

Disclosure

The authors report no conflicts of interest in this work.

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