Original Article

Thai Journal of Pharmaceutical Sciences

Development of health-related quality of life questionnaire for patients on continuous drug use

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Received: Oct 06, 2019
Accepted: Apr 15, 2020
Published: May 15, 2020

ABSTRACT

Background: Health-Related Quality of Life (HRQoL) instruments has become as a principal indicator of the effectiveness of medication treatment especially in case of lifelong therapy. **Objectives:** The purposes of the study were to develop a quality of life (QoL) questionnaire for Thai patients with continuous drug use (CDU-QoL) and to test the psychometric properties of the instrument. **Methods:** The development process comprised instrument development, expert review, factor analysis, and psychometric property test. **Results:** Construction of the instrument was initiated using qualitative methodology resulting in tentative ten domains and an initial pool of 42 items. Content validity was evaluated by nine experts. After pilot test, factor analysis, and psychometric property tested, the final version was 27-item CDU-QoL with five levels on a Likert scale consisting of six domains: Daily activities, mental activities, social activities, family support, adverse drug reaction, and positive outcomes. The overall coefficient alpha of this instrument was 0.922. Criterion-related validity was supported by positive correlations with Short Form Health Survey version 2.0 (SF-36v2), EuroQol 5-dimension-3-level (EQ-5D3L), and medication adherence scale. **Conclusion:** These analyses provide preliminary evidence that supports the validity and reliability of the CDU-QoL questionnaire for patients with continuous drug usage.

Keywords: Continuous medication usage, quality of life, reliability, validity

INTRODUCTION

Chronic diseases continue to be the main cause of mortality and morbidity worldwide.[1] Appropriate long-term use of medicines in patients with chronic diseases is important to relieve symptoms, reduce relapse rates, and help slow disease progression,[2,3] thereby improving health-related quality of life (HR QoL).[4] However, around 50% of patients with chronic disease do not fully adhere to their medication as prescribed[5] and ultimately lead to low QoL.[6-8] Thus, uninterrupted medication use by patients is a factor that could improve their well-being.

At present, QoL questionnaires have been developed as either generic QoL or disease-specific questionnaires. Generic QoL instruments (e.g., 36-Item Short Form Health Survey [SF-36]; and EuroQol-5 dimensions [EQ-5D]) have been created for a wide range of populations, diseases, and interventions, but often lack enough sensitivity to detect differences of QoL within patients who have specific diseases.[9] In such conditions, specific QoL tools (e.g., Functional Assessment of Cancer Therapy-Breast scale, QoL in Epilepsy-89) are more responsive to changes in clinical status than generic tools.[9-13] Furthermore, QoL questionnaires exclude any domain on medication use[14,15] but rather assess QoL in chronic disease in general[16] or in specific diseases. Few include well-being resulting from medication use in general[17] or a specific drug class.[18] However, patients with chronic diseases are usually prescribed multiple drugs and often multiple drug classes. Murawski's questionnaire measures QoL related to medication use but reported to have poor validity.[19] Therefore, we aimed to develop a questionnaire that measures QoL of patients with chronic diseases who need continuous drug usage (CDU-QoL) and to test the psychometric properties of our questionnaire.

MATERIALS AND METHODS

The development process of the CDU-QoL questionnaire for patients with chronic disease was adapted from the standard questionnaire development guidelines and methodologies used in the previous studies.[9,20] This process involved three steps as follows: (1) Questionnaire development, (2) expert review of the instrument, and (3) psychometric property testing of the

final questionnaire. In this study, chronic diseases was defined as diseases of long duration and generally slow progression.[21]

Step 1: Instrument Development

The objectives were to: (1) Define CDU-QoL, (2) identify instrument domains, (3) generate items for each domain, and (4) design the instrument format and response choices.

In this study, QoL was based on Murawski and Bentley's HR QoL concept and pharmaceutical therapy-related QoL (PTR QoL) concept.[17] It was defined as the patient's sense of well-being related to physical, mental, emotional, and social function, and satisfaction with their life through the process of perception and self-assessment regarding continuous medication use, either positively or negatively. Here, CDU is defined as continuing the treatment throughout the prescribed duration.[22]

The domains used were gathered from: (i) The domains from the definition, (ii) domains from a pharmaceutical literature review, (iii) expert opinions, and (iv) semi-structured interviews with patients about their experiences of continuous medication. A literature review searched the following databases: MEDLINE, PubMed, ProQuest, ScienceDirect OnSite, and SPRINGER using the search terms: "QoL," "well-being," "health status," "happiness," "satisfaction," "taking continuous medication," "instrument development," "tool," "questionnaire," and "psychometric testing." Reference lists of discovered articles were also searched.

A pool of items for each domain was obtained from a semi-structured interview of 24 patients on continuous use of medication recruited from the Deja Hospital outpatient clinic (Bangkok, Thailand) about how their well-being was affected by the medication regime. Their verbal responses were extracted, then categorized as domains and question items generated.

The CDU-QoL questionnaire was designed as a self-assessment tool. The measurement scale for each item was on a 5-point Likert scale with "1= Not at all, 2= A little, 3= A moderate amount, 4= A lot, and 5= An extreme amount" for positive QoL statements and reverse score of 5–1 for statements that negatively impact on QoL.

Step 2: Expert Review of the Instrument

To examine content validity of the CDU-QoL questionnaire, expert opinion was sought to assess content of each item for relevance and representative of its domain construct.

Nine experts who had experience of questionnaire design and caring patients with chronic disease, including three social sciences educators, two clinical pharmacy educators, three hospital pharmacists, and one community pharmacist, were recruited to examine content validity of the CDU-QoL questionnaire. They assessed each proposed item for clarity, its relevance, and representativeness of its domain in the context of continuous medication for chronic disease. Each proposed item was awarded a content validity index (CVI) on a four-point ordinal scale as follows: 1 = not relevant, 2= unable to assess relevance without item revision or the item needs such revision that was no longer relevant, 3= relevant, but needing minor alteration, and 4= very relevant. For each item, the CVI was computed by summing the total of all scores of 3 or 4, divided by the total number of experts.[23,24] The threshold for content validity was when seven of the nine experts awarded a grade of 3 or 4, i.e., a CVI more than 0.78 and thus retained in the questionnaire. Items failing the 0.78 threshold were revised. Experts were also asked to suggest any additional components that should be added to the questionnaire and to suggest any modifications for existing items (e.g., reword, revise, and grammatical corrections).

Step 3: Psychometric Property Testing of the Instrument

The resultant CDU-QoL questionnaire was tested for its psychometric properties by running a pilot evaluation (pretesting) followed a large-scale study.

Pilot test (pretesting)

The study goals were to assess (a) the clarity of each item, redundant items with similar meaning and to eliminate any items causing confusion, (b) the time subjects spent to complete the CDU-QoL questionnaire, (c) the internal consistency of items within each domain, and (d) problems related to the questionnaire layout.

Another 30 participants on CDU were recruited from the Deja Hospital outpatient clinic. They were told: The overall purpose of the study, its risks and benefits, the time needed to complete the questionnaire, that their answers would remain confidential and anonymous, and that they could discontinue at any time. Consent was by verbal agreement. There was no payment for participation. The items were evaluated for face validity including (1) the clarity (e.g., ambiguous words, inability to answer the questionnaire, and redundant items). (2) easy comprehension (time spent was recorded), (3) the layout and style, and (4) to provide verbal suggestions that might be incorporated in a modified questionnaire.

Large study testing

The next version of the questionnaire was assessed for its psychometric properties, i.e., reliability and construct validity.

Setting and participants

A cross-sectional study using the pilot-modified version of CDU-QoL questionnaire was carried out between March and May 2013 in the outpatient departments of the Police General Hospital (government run) and the Deja Hospital (private). Inclusion criteria were: Aged 20 years or older and prescribed one or more drugs for chronic disease for at least 6 months before data collection. Exclusion criteria were pregnancy, history of already receiving a psycho-active drug, unable to complete self-reported surveys (e.g., cognitive deficits), and unable to understand the Thai language. Before study entry, informed consent was by verbal agreement to respond. The sample size was determined by criteria of factor analysis.[25] As a general rule, the minimum cohort size should be at least five-fold more than the number of variables to be analyzed, while ten-fold is more acceptable. Thus, a 30-item questionnaire should recruit 300 participants and be adequate for exploratory factor analysis (EFA).[26]

Statistical Analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences software (SPSS for Windows version 17.0, SPSS Co., Ltd., Bangkok Thailand). The level of significance for any statistical tests was set at $\alpha = 0.05$. Demographic characteristics of the participants (e.g., age, sex, marital status, education, occupation, health system, and income) and characteristics of participant drug use were summarized by descriptive statistics (mean, standard deviation, range, frequency, and percent). Reliability and validity data for the existing measures were also computed. List wise data exclusion was used in all statistical analyses, i.e., any participant having a missing value for any variable was omitted from the entire data analysis. Item frequency of CDU-QoL was displayed as the percentage of scores at the extremes of the scaling range, as well as, the maximum possible score (ceiling effect) and the minimum possible score (floor effect).

Psychometric testing was evaluated as follows:

Construct validity

Since no prior study in Thailand on QoL of patients with continued medication use, the component domains of CDU-QoL were never determined. The researcher then used EFA with principal axis factoring (PAF) to reduce dimensionality as a measure of construct validity. The Promax Rotation was used with the assumption that the questionnaire items were correlated. The number of factors was determined by eigenvalues >1. For defining items associated with a given factor, factor loadings >0.4 on all factors were used as a cutoff point. Items that were cross-loaded on multiple factors with loadings >0.4 were also excluded from the instrument according to a suggested cross loading rule.[12,27] The adequacy of the variable items for factor analysis was assessed using the Kaiser-Meyer-Olkin (KMO) index, Bartlett's Sphericity Test (BST) and the measures of sampling adequacy (MSAs). KMO and MSA values were considered satisfactory if they were ≥0.6 and BST with a level of statistical significance of $P < 0.05$.[25] The next step was item selection for each factor that based on methodology prior studies.[11,28]

Criterion validity

The data were assessed by Pearson's product moment correlation coefficient between the studied questionnaire, CDU-QoL questionnaire, and the EQ5D3L in Thai, the SF-36V2 in Thai, SF6D utility index derived from SF-36V2, adherence self-reported scores. The strength of correlation[29] was classified using r value with r = 0.0–0.2 as very weak to negligible correlation, 0.21–0.34 as weak, low correlation, 0.35–0.5 as moderate correlation, and >0.5 as strong, high correlation.

Adherence by self-reported scores, self-reported modified adherence score, consisted of five questions that determined their feelings about continuous medication-taking in the past 4 weeks and rated on a 5-point Likert scale (with 1= never, 2= rarely, 3= sometimes, 4= often, and 5= always). Scores are summed, and totals ranged from 5 to 25, with higher scores indicating higher adherence by self-report. These items were as follows:

1. You always take your medications continuously for the entire period as prescribed
2. You take each medication at the correct/suggested dose according to your doctor's instructions
3. You continue all your medications completely at every meal as prescribed
4. You take continuous medication on time according to order instructed by your doctor at each meal
5. You get all prescriptions refilled after every doctor appointment.

A single item (the visual analog scale: VAS) was used to assess overall adherence; 100-point VAS[30] with 0 indicating "absolute non-adherence" and 100 "excellent adherence."

Reliability

Two methods were used to estimate reliability: Item analysis and Cronbach's alpha (α). A Cronbach's α coefficient value of 0.70 or greater would be considered to represent a questionnaire with acceptable internal consistency.[9,31,32] Internal reliability was assessed on the items constituting each domain in the CDU-QoL questionnaire. Items were removed from each domain if they did not meet the three following criteria: (1) Coefficient alpha or Cronbach's alpha coefficient ≥0.70, (2) corrected item-total correlation ≥0.30, and (3) alpha if the item deleted < Cronbach's alpha coefficient.

Ethical Disclosures

Ethical approvals were gained from the Chulalongkorn University Institutional Review Board and Ethics Committee of the Police General Hospital (protocol review no.12-33-005). All participants were informed that they could stop their participation at any time. Consent by action was allowed as informed consent by patients.

RESULTS

Questionnaire Development and Expert review of the Questionnaire

The initial draft CDU-QoL version 1 contained 42 items in ten domains. After evaluating content validity by the experts, the version 2 was created by removing 12 items in seven domains by the construct validity test. Many experts queried the term "continuous medication" and its meaning was added to questionnaire preamble as a "continuing period of at least 6 months on prescribed medication for treatment of a chronic condition." They were also unclear about the term "taking medication" and changed to "using medication" since "using" covered administering medicines orally and by other routes including external use of medication, for example, eye drop and inhaler.

Psychometric Property Testing

Pilot test (pretesting)

All 30 recruits were tested and no item was eliminated from the questionnaire. All respondents understood how to complete the questionnaire and time spent varied from 10 to 35 min, mean time 20.3 ± 7.3 min (SD).

Large study testing.

Baseline Characteristics

The 530 respondents were aged 21–81 years, mean 50.13 (SD ±8.95 years), 55.7% were female, 62.6% married,

Table 1: Demographic and clinical characteristics the participants

Parameter	Total sample (*n*=530)
Mean age, years (±SD)	50.13 (8.95)
Female, *n* (%)	295 (55.7)
Highest level of regular school education completed, n (%)	
Primary school or less	131 (24.7)
Secondary school	174 (32.8)
Diploma	78 (14.7)
Bachelor degree	134 (25.3)
Higher bachelor degree	13 (2.5)
Marital status, *n* (%)	
Single	88 (16.6)
Married	332 (62.6)
Divorced/separated	65 (12.3)
Widowed	45 (8.5)
Occupation, *n* (%)	
Business owner	50 (9.4)
Employed daily	90 (17.0)
Government employee/State Enterprises	20 (3.8)
Company employee	303 (57.2)
Unemployed	30 (5.7)
Retired	34 (6.4)
Other	3 (0.6)
Monthly income (baht/month), *n* (%)	
No income	38 (7.2)
<5000	27 (5.1)
5000–10,000	188 (35.5)
10,001–20,000	194 (36.6)
More than 20,000	83 (15.7)
Health insurance, n (%)	
Civil servant medical benefit scheme	69 (13.0)
Universal coverage (gold card)	34 (6.4)
Social security scheme	423 (79.8)
Other	4 (0.8)
Chronic disease, *n* (%)	
Hypertension	352 (66.4)
Diabetes	227 (42.8)
Dyslipidemia	207 (39.1)
Cerebrovascular	10 (1.9)
Kidney	15 (2.8)
Asthma	14 (2.6)
Cardio	22 (4.2)
Other	105 (19.8)
Number of chronic diseases, *n* (%)	
1	203 (38.3)
2	250 (47.2)
3	63 (11.9)
4	12 (2.3)
5	1 (0.2)
6	1 (0.2)
Number of prescription medications, *n* (%)	
1	61 (11.5)
2	130 (24.5)
3	146 (27.5)
4	105 (19.8)
5	41 (7.7)
6	19 (3.6)
≥7	28 (5.3)

and 32.8% educated to secondary level. The most common diseases were hypertension (60%), diabetes (42.8%), and dyslipidemia (39.1%). Participants were prescribed 1–15 drugs as continuous medication, mean 3.3 (SD ±1.90 items): One drug (11.5% of participants), two drugs (24.5%), three drugs (27.5%), four drugs (19.8%), and five or more drugs (5.3%). Other parameters are shown in Table 1.

Construct Validity

EFA was used to examine the factor structure for the 30-item CDU-QoL. Bartlett's test for sphericity was significant for CDU-QoL ($\chi 2$ = 11,019, df =435, $P < 0.001$), showing item multivariate normal distribution, and the correlation matrix was suitable for factor analysis. Promax Rotation with KMO measure of sampling adequacy was 0.924 for CDU-QoL, large enough to perform factor analysis. Two items were removed because of the extraction criteria (loadings less than 0.4 on all domains and cross-loaded more than one factor).

Item analysis and scales

Item analysis was conducted on the shorter 28-item CDU-QoL by Cronbach's alpha, corrected item-total correlation and alpha if item deleted.[31]

All 28 items had corrected item-total correlation ≥0.30. The reliability coefficient of each domain determined by Cronbach's alpha coefficient was ≥0.70 a threshold considered to be an acceptable level of internal consistency. However, two items did not meet all Cronbach's criteria:

1. The item on *"a burden with extra cost"* was not relevant to its domain about adverse drug reactions. The deletion of item improved Cronbach's reliability (alpha =0.89) for the domain
2. Another item on *"worried about forgetting or mistaking the medication"* was under the domain related to travelling. However, deleting this item would lead to the domain containing only two question items. The previous studies[11,32] recommended at least 3–4 items per domain are needed interpret factor analyses. This item was thus retained in the questionnaire resulting in a 27-item CDU-QoL.

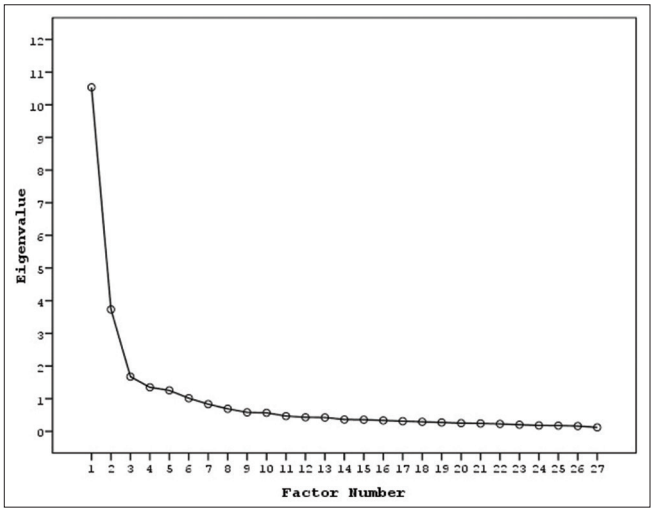

Figure 1: Scree plot of the 27-item continuous drug use-quality of life questionnaire

To optimize interpretation, an item analysis and a Promax rotation with re-run of the EFA were performed for the 27-item CDU-QoL questionnaire. The loading criteria of 0.40 were used as the cutoff point. The KMO statistic (0.919) was adequate (i.e., >0.6) and Bartlett's test of sphericity was significant ($\chi 2$ = 11,019, df =435, P < 0.001). Using the scree plot (consisted of placing and eigenvalues graph against a number of items present) to determine a cutoff point.[9] Reading off five or seven domains on the scree plot [Figure 1] may be appropriate where the percentage of total variance explained ranged between 68.7 and 75.5, respectively. Then, the final EFA presented 27 items in sxi domains and could explain 72.4% of the total of the questionnaire variability [Table 2]. The factor plot in rotated factor space of the 27-item CDU-QoL shows the loadings for 27 items on the six factors [Figure 2].

The final consideration was to assign each domain with a construct name. The 27-item CDU-QoL questionnaire with overall domain descriptions is shown in Table 2.

1. Domain 1 (*"social activities"*) measured perceived impact of continuous drugs use on personal relations, social interactions and involved social roles, avoidance or reduction of typical social activities. This domain accounted for most of the variance [Table 2].
2. Domain 2 (*"mental activities"*) asked about perceived psychological and emotional function: Indicators of emotional state, boredom, feeling of downheartedness, depression, and perceived impact of drug use on general health (being an unhealthy person)
3. Domain 3, comprising 6.20% of variance was named as *"positive outcomes,"* and contained 4 items whose factor loadings were 0.77–0.95. The domain items measured perceived benefits of continuous drugs use on both positive psychological impacts (confidence because of taking continuous drug, and effectiveness drug use) and physical impacts (improve symptoms, ability to perform regular work-related tasks, having a normal life)
4. Domain 4 explained 5.0% of the variance and named *"adverse drug reaction."* It contained 4 items and factor loadings ranged between 0.55 and 0.88. This consisted of items related to perceived impact of continuous drugs use which related directly side effects of medication. In addition, it also concerned with perceived emotional functioning, role functioning (decrease work performance)
5. Domain 5 was labeled *"daily activities,"* it could explain 4.6% of the variance, had 5 items, and factor loadings ranged between 0.33 and 0.84. This domain measured perceived impact of continued drug use on activity of daily living
6. Domain 6 was named *"family support,"* accounting for 3.8% of the variance had 3 items, and factor loadings were 0.42–1.01. These items measured perceived impact of drug use on a need for family and caregiver support.

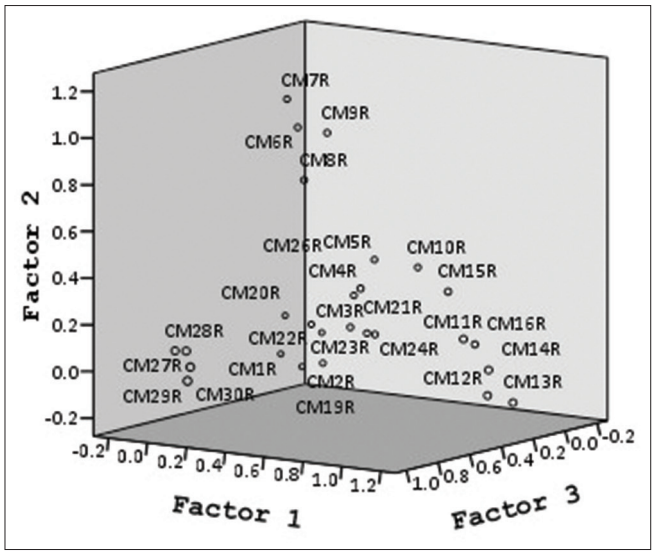

Figure 2: Factor plot in rotated factor space of the 27-item version. CM1R to CM27R codes items 1-27

Reliability Analysis

Cronbach's α was also applied to the whole 27-item CDU-QoL questionnaire [Table 3]. Internal consistency was 0.922 which is acceptable for a new questionnaire. The reliability of each domain was found as follows: "Social activities" (α =0.912), "mental activities" (α =0.911), "positive outcomes" (α =0.901), "adverse drug reaction" (α =0.890), "daily activities" (α =0.782), and "family support" (α =0.783). In addition, all 27 items of CDU-QoL questionnaire had item-total correlations ranging 0.498–0.839.

Criterion-related Validity Comparisons

The SF-36V2 questionnaire

In this study, the assumption was that domain scores of the CDU-QoL questionnaire would be significantly correlated with scores for similar domains from the SF-36V2 and EQ5D questionnaires [Table 4]. The correlations between the CDU-QoL total score and all SF-36V2 domains, physical component summary (PCS), and mental component summary (MCS) varied from moderate to strong (r = 0.35–0.56). Regarding the correlations of each domain of the CDU-QoL: "Daily activities," "family support," and "positive outcomes" were poorly associated with PCS and MCS (r = 0.11–0.34). "Mental activities" correlated moderately between PCS and MCS, r = 0.36 and 0.51 (P < 0.01), respectively.

The EQ5D questionnaire

The CDU-total score and CDU-VAS were positively associated with general health status reported on the EQ5D-VAS (r = 0.21; P < 0.01, r = 0.43; P < 0.01, respectively), as hypothesized [Table 4]. The correlations between CDU-Total score and each EQ-5D3L domain were found to be weak (r = 0.12 to 0.27; P < 0.01), [Table 5]. Resulting positive direction of the coefficients can be explained by the fact that higher scores on the CDU-QoL display better well-being, while higher scores on the EQ-5D-VAS display better health.

Questionnaire about adherence to medication

The correlations between CDU-QoL domains and scores for adherence to medication were weak although statistically significant (r = 0.10–0.22; P < 0.01) except "daily activities" domain [Table 4]. The CDU-QoL VAS was moderately correlated with adherence VAS at 0.45. Although the CDU-total score was positively correlated with the "adherence" score, it was low.

Table 2: Factor structure and loadings of the 27-item continuous drug use-quality of life for 530 participants using principal axis factoring and Promax Rotated method

Item#	Item statement	Factor					
		1	2	3	4	5	6
		Social activities	Mental activities	Positive outcomes	Adverse drug reaction	Daily activities	Family support
1	Regular medication causes me to lose my confidence when participating in social activities	1.02	−0.18	−0.01	0.03	−0.05	−0.04
2	I do not want other people to know that I have to take lots of medicines	0.94	−0.04	−0.07	0.06	−0.14	−0.09
3	Taking medication deflects me from some social activities (e.g., party)	0.92	−0.15	−0.05	0.04	0.03	−0.04
4	I feel embarrassed when taking medication in the presence of friends and colleagues	0.81	0.08	−0.07	0.01	−0.14	0.03
5	Continuous medication prevent me going away	0.75	0.03	0.08	−0.03	0.04	0.01
6	Continuous medication makes it difficult for me leave the house	0.61	0.24	0.08	−0.02	0.02	−0.02
7	I am worried about forgetting or mistaking the medication	0.39	0.30	0.16	−0.18	0.15	0.04
8	Daily medication makes me bored	−0.13	1.01	−0.03	−0.04	−0.09	0.01
9	The repetitiveness of continuous medication creates a sense of hopelessness	−0.06	0.89	−0.04	0.06	0.02	−0.06
10	I feel depressed because of continuous medication	0.07	0.88	−0.01	0.04	−0.13	−0.03
11	Taking medication continuously makes me appear to be unhealthy	−0.01	0.68	−0.07	0.15	−0.02	0.01
12	I am worrying all the time about timing my medication	0.21	0.33	0.10	-0.17	0.33	0.03
13	Adhering to the regular medication gives confidence that symptoms will not relapse	−0.11	0.02	0.95	0.05	−0.07	0.02
14	Maintaining the regular medication normalizes my daily routines	−0.06	−0.02	0.87	0.04	−0.04	−0.01
15	The regular medication routinely helps avoid work absences or allows activities that I want to do	0.08	-0.06	0.80	0.01	0.01	−0.03
16	The continuing medication improves my symptoms	0.04	−0.06	0.77	−0.04	0.03	−0.01
17	The side effects of medication decreases my efficiency to work	−0.02	0.00	0.05	0.88	0.03	0.03
18	Side effects from the medication makes me feel even more sick/ill	−0.00	0.05	−0.03	0.74	0.07	0.00
19	The side effects disrupts my daily life	0.29	0.03	0.02	0.63	−0.01	−0.03
20	The side effects from routine medication are annoying	0.15	0.18	0.05	0.55	0.01	0.00
21	Taking medication continuously makes me wary of some types of foods	−0.05	−0.13	−0.04	−0.07	0.84	−0.02
22	Taking medication continuously makes me careful about non-routine medication	−0.16	−0.09	−0.03	0.19	0.80	−0.09
23	My time is wasted by having to organize the medication regime	0.20	0.06	−0.03	0.04	0.41	0.13
24	My daily life is disrupted by having to take medication continuously	0.25	0.23	−0.03	0.05	0.33	0.04
25	I need a career to help with looking after my medication	0.05	−0.11	−0.03	−0.08	−0.05	1.01
26	People around me need to remind me to take the medication	−0.17	0.07	0.00	0.11	−0.03	0.68
27	Regular medication is a burden for my family	0.25	0.04	0.01	0.19	0.01	0.42
	Eigenvalue	10.53	3.73	1.67	1.35	1.25	1.01
	% of variance explained	39.02	13.81	6.20	5.00	4.64	3.75

The numbers in bold represent factor loadings > 0.4 and are items that are adequately associated with a specific domain/factor of the 27-item CDU-QoL questionnaire. CDU-QoL, the continuous drug use-quality of life questionnaire

Table 3: Reliability and descriptive statistics of the 27-item continuous drug use-quality of life questionnaire (n=530)

Item	Mean of 530 (domain)	SD	Alpha	Corrected item total correlation	Alpha if item deleted	Standardized item alpha
Reliability of 27 items = 0.922			0.922			0.925
Domain 1: Social activities (7 items)	(4.03)		0.912			0.916
Item 7	3.35	1.17		0.576	0.920	
Item 2	4.33	0.97		0.755	0.897	
Item 4	4.29	0.95		0.755	0.897	
Item 6	3.89	1.00		0.751	0.897	
Item 5	4.06	0.97		0.766	0.896	
Item 3	4.11	0.97		0.769	0.895	
Item 1	4.20	0.91		0.810	0.892	
Domain 2: Mental activities (4 items)	(3.80)		0.911			0.912
Item 11	3.73	1.15		0.733	0.908	
Item 8	3.77	1.10		0.808	0.881	
Item 10	3.90	1.07		0.826	0.875	
Item 9	3.81	1.09		0.827	0.874	
Domain 3: Positive outcomes (4 items)	(3.83)		0.901			0.904
Item 15	3.63	1.14		0.753	0.888	
Item 16	3.81	0.94		0.754	0.881	
Item 14	3.98	0.94		0.789	0.869	
Item 13	3.91	0.97		0.839	0.850	
Domain 4: Adverse drug reaction (4 items)	(4.18)		0.890			0.890
Item 20	4.08	0.97		0.732	0.869	
Item 18	4.24	0.86		0.735	0.867	
Item 19	4.20	0.90		0.767	0.855	
Item 17	4.20	0.94		0.802	0.841	
Domain 5: Daily activities (5 items)	(3.30)		0.782			0.787
Item 22	2.89	1.17		0.498	0.763	
Item 21	2.59	1.15		0.507	0.759	
Item 12	3.33	1.21		0.567	0.739	
Item 24	3.90	1.01		0.617	0.725	
Item 23	3.79	1.02		0.618	0.724	
Domain 6: Family support (3 items)	(4.15)		0.783			0.790
Item 26	3.90	1.06		0.588	0.761	
Item 27	4.30	0.82		0.590	0.747	
Item 25	4.27	0.92		0.713	0.606	

CDU-QoL: The continuous drug use-quality of life questionnaire, SD: Standard deviation

DISCUSSION

The CDU-QoL questionnaire has internal consistency, reliability, and preliminary evidence of validity (content, construct, and criterion). We present this as a self-administered questionnaire to evaluate the impact of continuous drug on QoL of patients with chronic disease.

Characteristics of the Participants

The target population was heterogeneous for age, sex, education, incomes, health insurance, number of diseases, number of medications prescribed, etc. The results from this diverse population suggest that our questionnaire can be generalized across different chronic disease. They were dominated by hypertension (60%), diabetes (42.8%), and dyslipidemia (39.1%), in agreement with the previous studies on Thais.[33,34] The sample size comprised 530 participants giving strength to the EFA.[35]

Psychometric Tests

Content validity test

Nine experts evaluated content validity which was statistically justifiable and enough to reduce erroneous

Table 4: Concurrent validity of the CDU-QoL questionnaire with the SF36V2, EQ5D3L, adherence scores, and adherence-VAS (Pearson' coefficients correlation: $n = 530$)

Variable	SF36V2 Summary Score		SF36V2 Sub-domains								EQ5D3LThai score	EQ5D -VAS	Adherence scores	Adherence VAS
	Physical component summary	Mental component summary	Physical function	Role physical	Bodily pain	Social functioning	General health perception	Vitality	Role emotional	Mental health				
CDU-QoL domains														
Daily activities	0.15**	0.31**	0.19**	0.31**	0.20**	0.31**	0.07	0.08	0.38**	0.24**	0.07	0.06	0.01	0.05
Mental activities	0.36**	0.51**	0.32**	0.42**	0.37**	0.46**	0.38**	0.40**	0.46**	0.49**	0.32**	0.23**	0.17**	0.23**
Social activities	0.49**	0.23**	0.22**	0.40**	0.30**	0.48**	0.21**	0.25**	0.47**	0.42**	0.14**	0.11*	0.10*	0.09
Family support	0.24**	0.34**	0.23**	0.35**	0.26**	0.35**	0.16**	0.20**	0.37**	0.29**	0.18**	0.06	0.18**	0.14**
Adverse Drug Reaction	0.32**	0.52**	0.30**	0.41**	0.37**	0.49**	0.32**	0.38**	0.48**	0.47**	0.26**	0.16**	0.17**	0.27**
Positive outcomes	0.20**	0.11**	0.13**	0.06	0.13**	0.09*	0.28**	0.29**	0.01	0.16**	0.19**	0.20**	0.22**	0.42**
CDU-Total score	0.37**	0.56**	0.34**	0.48**	0.40**	0.53**	0.35**	0.40**	0.53**	0.51**	0.29**	0.21**	0.21**	0.27**
CDUQoL-VAS	0.23**	0.14**	0.17**	0.06	0.17**	0.12**	0.33**	0.24**	0.09*	0.16**	0.21**	0.43**	0.12**	0.45**

*$P<0.05$, **$P<0.01$ correlation coefficients with value 0.21–0.34 as weak correlation, 0.35–0.50 as moderate, and >0.5 as strong correlation. CDU-QoL: The continuous drug use-quality of life questionnaire, CDU QoL-VAS: Continuous drug use-quality of life-the visual analogue scale, SF36V2: The Short Form Health Survey version-2.0, PCS: Physical component summary, MCS: Mental component summary, PF: Physical function, RP: Role physical, BP: Bodily pain, SF: Social functioning, GH: General health perception, VT: Vitality, RE: Emotional role functioning, MH: Mental health, EQ5D3L: The EuroQol five-dimensions – three-level questionnaire, EQ5D-VAS: EuroQol visual analogue scale, adherence VAS: Adherence visual analogue scale

Table 5: Pearson' correlation coefficients between CDU-QoL and EQ5D3L domains (n=530)

Variable	EQ5D3L score: Domains				
	Mobility (MO)	Self-care (SC)	Usual activities (UA)	Pain/discomfort (PD)	Anxiety/depression (AD)
CDU-QoL domains					
Daily activities	0.08	0.10*	0.07	0.06	0.20**
Mental activities	0.15**	0.21**	0.18**	0.26**	0.28**
Social activities	0.01	0.20**	0.09*	0.10*	0.21**
Family support	0.09*	0.19**	0.14**	0.11*	0.16**
Adverse drug reaction	0.12**	0.23**	0.15**	0.21**	0.16**
Positive outcomes	0.22**	0.17**	0.15**	0.09*	0.05
CDU-total score	0.12**	0.27**	0.20**	0.21**	0.24**
CDUQoL-VAS	0.16**	0.09*	0.19**	0.18**	0.08

*P<0.05, **P<0.01 correlation coefficients with value 0.21–0.34 as weak correlation, 0.35–0.50 as moderate, and >0.5 as strong correlation. CDU-QoL, Continuous drug use-quality of life, CDUQoL-VAS: Continuous drug use-quality of life-the visual analogue scale, EQ5D3L: The EuroQol five-dimensions – three-level questionnaire; Dimensions: MO: Mobility, SC: Self-care; UA: Usual activities, PD: Pain/discomfort, AD: Anxiety/depression

conclusions. This exceeds the minimum of five experts proposed by Lynn[23] in any one area of interest. The maximum number of experts has yet to be established but it should not exceed ten. In niche areas where experts are limited, then three are recommended.[23,36] For face validity, CDU-QoL questionnaire was completed by all the 530 participants without intervention and thus suited to unattended self-administered.

Construct validity

Factor loadings and item selection: Selecting a PAF for factor analysis with a Promax Rotation was the simplest possible method to define domain structures.[26] We assumed that the CDU-QoL questionnaire had correlations between domains, so selecting this oblique rotation was appropriate because it produced solutions with an improved simple structure thereby allowing the factors to correlate. According to earlier QoL studies, domain scores were found to be correlated and not independent of each other, then direct oblimin and Promax would be appropriate.[11,28] As shown in Table 2, exclusion criteria for items with loadings <0.4 and/or cross loadings of ≥0.4 for more than one domain, which proved useful in interpreting the sequence of meanings within the domain structure. This is consistent with the previous studies[12,27,37,38] with problematic items. Items 12 and 24 loaded below 0.4 and drafted to capture on "daily activities" domain. However, despite not meeting the criteria, these two items were retained because they adequately contributed to the overall reliability of the "daily activities" domain (α >0.7). Item analysis by Cronbach's alpha and the re-run EFA until the satisfactory domain structure was obtained as the 27-item CDU-QoL questionnaire. This questionnaire named six domains as follows: (1) "Daily activities" (5 items), (2):mental activities" (4 items), (3) "social activities" (7 items), (4) "family support" (3 items), (5) "adverse drug reaction" (4 items), and (6) "positive outcomes" (4 items), and resulted in final communalities of 0.444–0.875. Although the communalities were <0.5, these items were retained because they share variances over the six domains, and these items have factor loadings >0.5. Thus, the 0.30 threshold of communalities can be applied.[39] Moreover, all of the communalities are sufficiently high to proceed with the rotation of the factor matrix. Considering examination of the scree plot and eigenvalues of >1, suggested that the six factors should be retained then continue with the analysis. The eigenvalue of the six retained domains was more than 1 (data not shown) along with approximately 72.4% of total variance. This supports the appropriateness of the six domains to explain the constructed of QoL questionnaire for patients prescribed continuous medication.

Reliability test

When reliability internal consistency by Cronbach's alpha (α) is high, i.e., 0.78–0.91, the value suggests that all items within a domain are scored consistently. In addition, all 27 items of CDU-QoL questionnaire have the item-total correlation ranged from 0.498 to 0.839 and these high values also imply internal consistency. This confirms that all of the items in each domain are homogeneous. For the "social activities" domain, the alpha value was high (α >0.90) reflecting the greater number of items.[40,41]

Criterion-related validity

Because no suitable standardized measure of QoL existed to compare our CDU-QoL questionnaire and there was no translated and validated questionnaire in Thai at the time of this study,[42,43] the generic SF-36V2 and EQ-5D3L questionnaires in Thai were used for criterion validity. We assumed that there were significant correlations between similar domains in each questionnaire. For the resulting criterion validity, the CDU-QoL total score was strongly correlated with the physical and MCS of the SF-36V2 and each sub-domain score, then our assumption about the validity of the questionnaire was acceptable. Strong associations were noted between the total score for CDU-QoL and three conceptually related SF-36 domains ("social function," "role emotion," and "mental health"); however, the highest correlation was found with the MCS [Table 4]. This association affirms the ability of our questionnaire to effectively measure the mental components of CDU-QoL. The CDU-QoL "daily activities" domain assessed physical activities specifically about how CDU impacts on daily activities and one might expect a weak correlation between PCS and all SF-36 sub-domains as observed. Established

AQ6

Box 1: The final version of the 27-item continuous drug use-quality of life questionnaire

Domain 1: Daily activities (5 items)
Item 1 Taking medication continuously makes me careful about non-routine medication
Item 2 Taking medication continuously makes me wary of some types of foods
Item 3 My time is wasted by having to organize the medication regime
Item 4 My daily life is disrupted by having to take medication continuously
Item 5 I am worrying all the time about timing my medication
Domain 2: Mental activities (4 items)
Item 1 The repetitiveness of continuous medication creates a sense of hopelessness
Item 2 Daily medication makes me bored
Item 3 Taking medication continuously makes me appear to be unhealthy
Item 4 I feel depressed because of continuous medication use
Domain 3: Social activities (7 items)
Item 1 I am worried about forgetting or mistaking the medication
Item 2 I feel embarrassed when taking medication in the presence of friends and colleagues
Item 3 Taking medication deflects me from some social activities (e.g., party)
Item 4 Regular medication causes me to lose my confidence when participating in social activities
Item 5 I do not want other people to know that I have to take lots of medicines
Item 6 Continuous medication makes it difficult for me leave the house
Item 7 Continuous medication prevent me going away
Domain 4: Family support (3 items)
Item 1 I need a career to help with looking after my medication
Item 2 People around me need to remind me to take the medication
Item 3 Regular medication is a burden for my family
Domain 5: Adverse Drug Reaction (4 items)
Item 1 Side effects from the medication makes me feel even more sick/ill
Item 2 The side effects of medication decreases my efficiency to work
Item 3 The side effects disrupts my daily life
Item 4 The side effects from routine medication are annoying
Domain 6: Positive outcomes (4 items)
Item 1 The continuing medication improves my symptoms
Item 2 The regular medication routinely helps avoid work absences or allows activities that I want to do
Item 3 Adhering to the regular medication gives confidence that symptoms will not relapse
Item 4 Maintaining the regular medication normalizes my daily routines

generic questionnaires (i.e., SF-36, WHOQOL-BREF, and EQ-5D) on medication related (MR) QoL also only yielded weak to moderate correlations[42,44] because the questionnaire targeted PTR QoL rather than HR QoL. Moreover, HR QoL has much wider scope such as disease burden, lifestyle, chronic patients experienced, illness duration or severity, and financial stresses.[45,46] Accordingly, we found weak correlations for both the EQ-5D Thai Score and EQ5D-VAS and poor associations between EQ-5D domains and CDU-QoL domains.

All the CDU-QoL domains showed weak correlations with the adherence score in this study. Here, two competing influences could be explained: (i) Positive impact as a consequence of the effectiveness of drug use and (ii) negative (i.e., side effects and social stigma) effects of drug adherence on QoL. Positive outcomes of CDU motivate the patients suffering adverse drug reactions while adhering to drug as prescribed has reduced QoL scores.[42,47] This supports earlier studies.[48,49]

Recently, there has been an increase in the development of QoL questionnaires related to medicine use, for example, the PTR QoL,[17,19] the patient-reported outcomes measure of pharmaceutical therapy for QoL (PROMPT-QoL),[43] the MRQoL,[48] the living with medicines questionnaire (LMQ),[50] and the MR Burden QoL (MRB-QoL).[38] The PROMPT-QoL only in a Thai version was carried out during this study. In addition, the PROMPT-QoL[51] was designed based on various concept of drug therapy related QoL (i.e., theories of QoL, HRQoL, PTRQoL, and patient-centered pharmaceutical care). A measure of psychometric properties[43,51] would be a useful addition to the construct validity test (i.e., known-groups validity and Rasch model). Although PROMPT-QoL and CDU-QoL have similar concepts (i.e., theories of QoL, HRQoL, and PTRQoL), they have only distinct domain names as positive domain. For instance, the different positive domain names were two domains of the PROMPT-QoL (named "satisfaction with medicine effectiveness" and "overall QoL") and one domain of the CDU-QoL (called "positive outcomes"). However, "family support" domain in this study was absent from the PROMPT-QoL, MRQoL, LMQ, and MRB-QoL.

Limitations of the Study

Designing purposive sampling may not be representative. Here, we recruited participants having chronic disease requiring continuous medication. These participants were drawn from two metropolitan hospital outpatient departments where most patients have non-communicable diseases dominated by cardiovascular and metabolic disease (hypertension, diabetes, and dyslipidemia). Responses to the questionnaire may vary: (i) For patients with cancer, HIV, TB, and chronic musculoskeletal pain where the effectiveness of their drugs and disease prognosis may differ, (ii) according to family and community support, (iii) with culture and language, especially those whose every-day conversation is not in Thai, and (iv) age group where expectations differ. In common with cross sectional surveys, this study might be subject to recall bias.

Recommendations to the Further Study

Known-group validity analysis should be studied further to determine the ability of the CDU-QoL questionnaire to discriminate among patients known to differ in their QoL for continuous medications usage.

Further research should apply factor analysis (CFA) to confirm domain structure that we extracted in the EFA

(exploring domain structure; how the items relate and group based on inter-variable correlations) and to confirm the number of latent variables underlining the items consistent with the expected number. Furthermore, responsiveness to change of this questionnaire should also be evaluated.

CONCLUSIONS

This study developed a QoL questionnaire for patients with CDU. Preliminary psychometric testing showed acceptable reliability and validity. Additional studies are needed to further validate other psychometric properties and to evaluate its responsiveness.

ACKNOWLEDGMENTS

This study was supported by the 90th Anniversary of Chulalongkorn University Fund (Ratchadaphiseksomphot Endowment Fund). The authors declare no conflicts of interest. Moreover, we would like to thank Dr. Matthew M. Murawski, Associate Professor, Pharmacy Administration, Purdue University, College of Pharmacy for helpful suggestions. We would also like to thank experts for their help in validation of questionnaire. Finally, the authors are most grateful to Associated Professor Chuenjid Kongkaew, PhD and C. Norman Scholfield, PhD for their valuable recommendations and language changes.

Supplement documentation [Box 1].

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