Clinical Science

Pedram Hamrah, MD, editor

Economic and Humanistic Burden of Dry Eye Disease in Europe, North America, and Asia: A Systematic Literature Review

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ABSTRACT Dry eye disease (DED) is a chronic and progressive multifactorial disorder of the tears and ocular surface, which results in symptoms of discomfort and visual disturbance. The aim of this systematic literature review was to evaluate the burden of DED and its components from an economic and health-related quality of life (HRQoL) perspective, and to compare the evidence across France, Germany, Italy, Spain, UK, USA, Japan, and China. PubMed, Embase, and six other resources were searched for literature published from January 1998 to July 2013. Of 76 titles/abstracts reviewed on the economic burden of DED and 263 on the HRQoL burden, 12 and 20 articles, respectively, were included in the review. The available literature suggests that DED has a substantial economic burden, with indirect costs making up the largest proportion of the overall cost due to a substantial loss of work productivity. In addition, DED has a substantial negative impact on physical, and potentially psychological, function and HRQoL across the countries examined. A number of studies also indicated that HRQoL burden increases with the severity of disease. Additional data are needed, particularly in Asia, in order to gain a better understanding of the burden of DED and help inform future health care resource utilization.

KEY WORDS Burden of disease, cost, dry eye disease, quality of life, systematic literature review

I. INTRODUCTION

Dry eye disease (**DED**) is a chronic and progressive multifactorial disorder of the tears and ocular surface, which results in symptoms of discomfort and visual disturbance, an unstable tear film, and potential damage to the ocular surface.[1,2] Two major subtypes of DED have been defined: aqueous tear-deficient DED and evaporative DED. Aqueous tear-deficient DED is subdivided into Sjögren syndrome (**SS**) DED and non-SS DED.[2] The most common cause of evaporative DED is meibomian gland dysfunction (**MGD**).[2] The prevalence of DED appears to increase with age, and has been reported to range from 5% to 33% of the adult population worldwide,[3,4] making it an important public health concern.

DED symptoms include irritation, stinging, dryness, ocular fatigue, and fluctuating visual disturbances.[1,2] These symptoms are likely to considerably impact a patient's quality of life (**QoL**), particularly because many patients will experience discomfort and visual problems over long periods of time. DED also is associated with an economic burden on patients, the health care system, and society as a result of direct medical costs relating to health care professional visits, pharmacologic therapies, and surgical procedures, and indirect costs owing to loss of work days and reduced productivity.

Accepted for publication November 2015.

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Sources of funding: This study was funded by Shire, who also provided funding for medical writing assistance. The authors had responsibility for the collection, analysis, and interpretation of data; the writing of the manuscript; and the decision to submit the manuscript for publication. Shire was involved in the study design and reviewed the manuscript for accuracy.

Marguerite McDonald has received consulting fees from Shire, Allergan, AMO-Abbott, Alcon, FOCUS Labs, Bausch and Lomb, RPS, TearLab, and TearScience. Michael S. Keith was an employee of Shire at the time this research was conducted and owns stock in Shire. Dipen A. Patel and Sonya J. Snedecor are employees of Pharmerit International, who were paid consultants to Shire in relation to this study.

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Abbreviations

CI	Confidence interval
DED	Dry eye disease
DEDIQ	Dry Eye Disease Impact Questionnaire
DEQ	Dry Eye Questionnaire
EQ-5D	EuroQol 5-Dimensions
ES	Effect size
ESS	Epworth Sleepiness Scale
ESSDAI	European League Against Rheumatism Sjögren's Syndrome Disease Activity Index
ESSPRI	European League Against Rheumatism Sjögren's Syndrome Patient-Reported Index
HADS	Hospital Anxiety and Depression Scale
HAQ	Health Assessment Questionnaire
HRQoL	Health-related quality of life
IDEEL	Impact of Dry Eye on Everyday Life questionnaire
IDEEL-SB	Impact of Dry Eye on Everyday Life questionnaire-symptom bother
MCS	Mental component summary
N/A	Not available
NEI-VFQ	National Eye Institute Visual Function Questionnaire
NSAID	Nonsteroidal anti-inflammatory drug
OR	Odds ratio
OSDI	Ocular Surface Disease Index
PCS	Physical component summary
QoL	Quality of life
RA	Rheumatoid arthritis
SF-8	8-item Short-Form Health Survey
SF-36	36-item Short-Form Health Survey
SG	Standard gamble
SLE	Systemic lupus erythematosus
SLR	Systematic literature review
SS	Sjögren's syndrome
TBUT	Tear film breakup time
TTO	Time trade-off
VAS	Visual analog scale
VFQ-25	25-item Visual Function Questionnaire
WHOQOL-BREF	World Health Organization Quality of Life-BREF scale
WLQ-J	Japanese version of the Work Limitations Questionnaire
ZSAS	Zung Self-Rating Anxiety Scale
ZSDS	Zung Self-Rating Depression Scale

Given the high prevalence of DED worldwide, the overall humanistic and economic burden is likely to be considerable. However, no systematic review of the evidence across geographic regions has been carried out to comprehensively assess this burden. Such a review is needed to improve understanding of the extent of and gaps in the current literature on the burden of DED and to help identify future research needs. We therefore conducted a systematic literature review to evaluate the burden of DED and its components from an economic and health-related QoL (**HRQoL**) perspective, and to compare the evidence across Europe (France, Germany, Italy, Spain, and the United Kingdom), North America (the United States) and Asia (Japan, China).

II. METHODS

A. Search Methods

PubMed/Medline, Embase, EconLit, Database of Abstracts of Reviews of Effects, National Health Service Economic Evaluation Database, Health Technology Assessment database, and Evidence Review Group reports were searched for literature on the economic or HRQoL burden of DED published from January 1998 to July 2013. The search was limited to published articles, supplemented with Internet searches to identify additional data when necessary (e.g., treatment guidelines not indexed in publication databases). Proceedings from conferences and clinical trial registries were not considered. The search terms for PubMed are shown in Table 1; other databases were searched using comparable terms.

B. Selection Criteria

Article selection criteria included English language articles and reports of original data relevant to the economic or HRQoL burden of DED in at least one of eight prespecified countries: China, France, Germany, Italy, Japan, Spain, the United Kingdom, and the United States.

Table 1. PubMed search terms*

Overall	("dry eye syndromes" [MeSH]) OR ("dry" [All Fields] AND "eye" [All Fields] AND "syndromes" [All Fields]) OR ("dry eye syndromes" [All Fields]) OR ((("dry" [All Fields] AND "eye" [All Fields]) OR ("dry eye" [All Fields])) AND (("disease" [MeSH]) OR ("disease" [All Fields]))) AND
Economic burden	("economics" [MeSH] OR "cost" [All Fields] OR "econ"* [All Fields] OR "burden" [All Fields] OR "healthcare resource use" [All Fields] OR "healthcare resource utilization" [All Fields] OR "indirect cost" [All Fields] OR "productivity" [All Fields]) OR
HRQoL	("qol" OR "quality of life" OR "patient satisfaction" [MeSH] OR "utility" OR "patient reported outcomes" OR "time tradeoff" OR "TTO" OR "activities of daily living" [All Fields] OR "ADL" OR "social impact")

* The "dry eye syndromes" MeSH includes "keratoconjuctivitis sicca," "Sjögren's syndrome," and "xerophthalmia." The "economics" MeSH includes "cost and cost analysis," "health care costs" (direct service costs, drug costs, employer health costs, hospital costs), "cost of illness," and "health expenditures."

ADL, activities of daily living; MeSH, Medical Subject Heading; TTO, time trade-off.

Search filters: humans, 15-year time frame (January 1998 to July 2013).

C. Data Collection and Extraction

Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed. One reviewer screened all titles and abstracts retrieved from the database searches, followed by full-text review of selected articles. References of systematic reviews and other articles were manually searched for additional appropriate citations. A standardized table was used to extract and record relevant data from selected publications, including author/year/journal, study objective, brief description of the study population, study outcome, key summarized findings, and study limitations.

III. RESULTS

Of 76 titles/abstracts reviewed on the economic burden of DED and 263 on the HRQoL burden, 12 and 20 articles, respectively, met the selection criteria as stated in the Methods section, and were included in the review (Figure). Tables 2 and 3 provide a summary of the literature identified. In a narrative synthesis of the results, findings on the economic burden of DED are presented according to total direct medical costs, treatment utilization/costs, and productivity loss and indirect costs, which are split further by geographic region. Of the 12 articles describing economic burden, only 4[5-8] gave the costs of over-the-counter preparations. Findings on the HRQoL burden of DED are presented by geographic region.

A. Economic Burden of DED

1. Total Direct Medical Costs

a. Europe

In the European countries of interest, our literature search identified a single source of data on direct medical costs. This was a cost analysis study in which the cost of DED for 2003 to 2004 was investigated in France, Germany, Italy, Spain, Sweden, and the United Kingdom. (Swedish data are not reported because Sweden was not among the prespecified countries for this review.)[9] Clegg et al performed a systematic literature search followed by interviews to evaluate the management practices of 23 randomly selected consultant ophthalmologists. The total annual cost of ophthalmologist-managed care for 1,000 patients with DED was estimated to range from US $0.27 million in France to US $1.10 million in the United Kingdom. This estimate includes the cost of specialist visits, diagnostic tests, and pharmacologic and surgical interventions, with the proportions of each differing across countries. The largest proportion of costs was accounted for by prescription drugs in Germany and the United Kingdom, diagnostic tests in Italy, and specialist visits in France and Spain.

b. United States

In the United States, a key source of data on the economic burden of DED (extracted for 2008) is a study by Yu et al among 2,171 patients with DED recruited from the Sjögren's Syndrome Foundation and Harris Interactive's Harris Poll.[8] With the assumption that treatment would not change significantly over 1 year, a decision analytic model was used to calculate the annual cost of managing a cohort of patients with DED. Direct costs consisted of ocular lubricant treatment, cyclosporine, punctal plugs, physician visits, and nutritional supplements. The annual total direct cost for DED to the US health care system was estimated to be US $782,673 for a cohort of 1,000 patients.[8] Factoring in the estimated number of individuals aged 50 years or older with DED in the United States (men, 1.68 million; women, 3.23 million[10,11]), the overall burden of DED on the health care system was calculated at US $3.84 billion. Direct costs also increased with disease severity; the average annual direct medical cost per patient for those with mild, moderate, and severe DED symptoms was estimated at US $678, US $771, and US $1,267, respectively.[8] In a second large

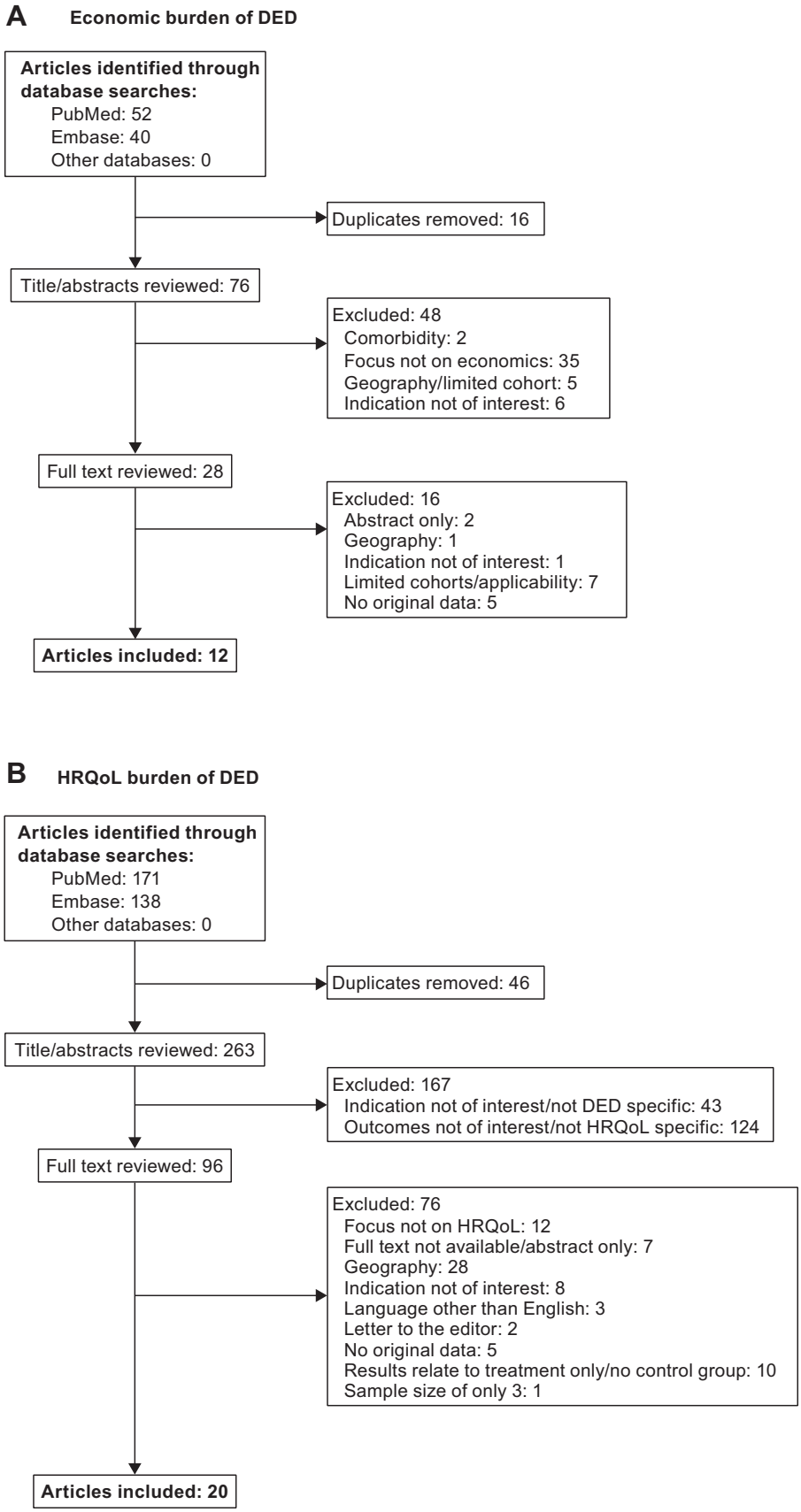

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram. DED, dry eye disease; HRQoL, health-related quality of life.

Table 2. Literature identified on the economic burden of DED

Reference	Country	Methods	Study population (n)	Year cost extracted (if stated)	Key cost data
Europe					
Clegg et al 2006[9]	France, Germany, Italy, Spain, and the United Kingdom	• SLR plus interviews of ophthalmologists	DED (model cohort, N ≈ 1,000)	2003–2004	• Direct cost analysis - Total annual cost of ophthalmologist-managed care for 1,000 patients with DED: France, US $273,000; Germany, US $536,000; Italy, US $645,000; Spain, US $765,000; United Kingdom, US $1,100,000 - Annual prescription drug costs per 1,000 patients with DED: France, US $22,000; Germany, US $227,000; Italy, US $51,000; Spain, US $256,000; United Kingdom, US $535,000
United States					
Brown et al 2009[5]	United States	• Cost-utility study of topical cyclosporine for treatment of DED	DED (N=877, of whom n=270 had SS)	2007	• Direct cost analysis - Total annual cost of topical cyclosporine per patient: US $1,276 - Total annual cost of preservative-free artificial tears per patient (Refresh® Lubricant Eye Drops, Allergan, Inc., Irvine, CA): US $96
Cross et al 2002[15]	United States	• Single-center retrospective chart review investigating clinical, economic, and patient-reported outcomes	DED (N=181)	1995–2000	• Total medication orders, including those used for DED (NSAIDs, antihistamines, artificial tears, ophthalmic antibiotics,

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Table 2. Literature identified on the economic burden of DED *(continued from previous page)*

Reference	Country	Methods	Study population (n)	Year cost extracted (if stated)	Key cost data
		related to topical cyclosporine A			and ophthalmic/antibiotic steroid combinations) decreased 55% after patients with DED were treated with topical cyclosporine A
Dalzell 2003[14]	United States	• Review article containing original data from a poster[53]	DED (N=74)	—	• Direct cost analysis - Cost of palliative medications, punctal plugs, and surgery for DED: US $357,050/500,000 lives • Indirect cost analysis - Patients with DED: average of 184 work days per year of reduced productivity; estimated annual cost of US $5,362 per patient
Fiscella et al 2008[12]	United States	• Retrospective claims analysis	Patients receiving topical cyclosporine (n=9,065) and punctal plugs (n=8,758)	2004–2005	• Direct cost analysis - Total annual health plan costs: US $3.05 million for topical cyclosporine cohort, US $3.28 million for punctal plug cohort (US $2.24 million for initial punctal plug procedures plus US $1.04 million for further procedures during follow-up) - Mean annual prescription cost paid by health plan per patient for topical cyclosporine cohort: US $336 - Mean annual cost per patient for

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Table 2. Literature identified on the economic burden of DED *(continued from previous page)*

Reference	Country	Methods	Study population (n)	Year cost extracted (if stated)	Key cost data
					punctal plug procedures in punctal plug cohort: US $375
Galor et al 2012[13]	United States	• Survey	Participants representative of the US population; using topical cyclosporine and/or blephamide (N=147)	2001−2006	• Direct cost analysis - Mean medication expenditure per patient, inflated to 2009 US $ amounts: 2001−2002, US $55 (n=29); 2003−2004, US $137 (n=32); 2005−2006, US $299 (n=86) - Mean annual DED medication expenditures per patient (females vs males): US $244 versus US $122; $P<.0001$
Hirsch 2003[16]	United States	• Review article containing original data from a congress abstract[54]	SS (N=N/A)	–	• DED symptoms interfered annually with leisure activities on 123 days • Patients absent from work for 5 days owing to DED symptoms/treatment and worked 208 days with symptoms
Patel et al 2011[17]	United States	• Cross-sectional, web-based survey • Participants were currently employed, had patient-reported physician-diagnosed DED, and OSDI score ≥13	DED (N=617), of whom had mild DED (n=124), moderate DED (n=132), severe DED (n=361)	–	• All three severity groups reported reduced productivity at work • Significantly greater reductions in productivity for moderate and severe DED versus mild DED ($P<.05$) • Impairment in ability to perform daily activities significantly greater for patients with severe

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Table 2. Literature identified on the economic burden of DED *(continued from previous page)*

Reference	Country	Methods	Study population (n)	Year cost extracted (if stated)	Key cost data
					versus mild/moderate DED ($P<.05$)
Reddy et al 2004[7]	United States	• Review of Medline articles plus clinician interviews	DED	2003	• Direct cost analysis (unit cost per visit/treatment [range]): - Ophthalmologist: US $68 (US $61–124) - General practitioner: US $48 (US $21–88) - Optometrist: US $68 (US $61–124) - Tear replacements: US $5–17 - Lubricant eye ointment: US $11–12 - Cyclosporine eye drops (single dose [32 vials]): US $115
Yu et al 2011[8]	United States	• Survey	DED (N=2,171)	2008	• Direct cost analysis (categories: ocular lubricant treatment, cyclosporine, punctal plugs, physician visits, and nutritional supplements) - Annual cost for patients seeking medical care: US $783 per patient (range, US $757–809); overall burden of DED for US health care system, US $3.84 billion - Annual medical cost per patient: mild DED, US $678; moderate DED, US $771; severe DED, US $1,267 • Indirect cost analysis - Annual cost to US society: US $11,302

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Table 2. Literature identified on the economic burden of DED *(continued from previous page)*

Reference	Country	Methods	Study population (n)	Year cost extracted (if stated)	Key cost data
					per patient and US $55.4 billion overall - In a cohort of workers, total productivity loss: ■ US $12,569−18,168 per year per patient ■ Mean lost no. of work days per year per patient: mild DED, 8.4 days; moderate DED, 3.7 days; severe DED, 14.2 days ■ Mean lost no. of work days per year per patient owing to affected performance: mild DED, 91 days; moderate DED, 94.9 days; severe DED, 128.2 days
Asia					
Mizuno et al 2012[6]	Japan	• Prospective cohort study	DED (N=118)	2008	• Direct cost analysis (categories: medical and drug costs, including costs related to artificial tear use and punctal plugs) - Total annual cost per patient: US $530 (¥52,467) - Annual drug costs per patient (± SD): US $323 ± $219 (¥32,000 ± ¥21,675) - Annual clinical costs per patient (± SD): US $165 ± $101 (¥16,318 ± ¥9961) - Annual costs of punctal plugs: US $42 ± $181 (¥4,149 ± ¥17,876)

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Table 2. Literature identified on the economic burden of DED *(continued from previous page)*

Reference	Country	Methods	Study population (n)	Year cost extracted (if stated)	Key cost data
Yamada et al 2012[18]	Japan	• Internet online survey based on the WLQ-J • Used the general consumer panel run by Cross Marketing Inc. (Tokyo, Japan)	Definitive DED (n=69), marginal DED (n=128), self-reported DED (n=80), controls (n=78)	2011	• Indirect cost analysis - Annual cost of work productivity loss associated with DED per patient: US $741 (¥59,758) • Cost of work productivity loss per patient: definitive DED, US $799; marginal DED, US $58; self-reported DED, US $1,036 • Degree of work performance loss: 5.65% (definite DED), 4.37% (marginal DED), 6.06% (self-reported DED), 4.27% (controls) • Productivity significantly lower in patients with self-reported DED versus controls ($P<.05$) - No significant differences in subscale scores of time management, physical demands, and output demands for patients with DED versus controls. However, mental/interpersonal score significantly lower in the definite DED ($P<.05$) and self-reported DED ($P<.01$) groups versus controls

CI, confidence interval; DED, dry eye disease; N/A, not available; NSAID, nonsteroidal anti-inflammatory drug; OSDI, Ocular Surface Disease Index; RA, rheumatoid arthritis; SLR, systematic literature review; SS, Sjögren's syndrome; WLQ-J, Japanese version of the Work Limitations Questionnaire.

Table 3. Literature identified on DED-related HRQoL

Reference	Country	Methods	HRQoL instruments used	Study population (n)	Key findings
			Europe		
Denoyer et al 2012[20]	France	• Prospective case-control study assessing time course of higher order aberrations/modulation transfer function	• OSDI	DED (n=40), controls (n=40)	• Significantly higher OSDI overall score/subscores in patients with DED versus controls ($P<.01$ for all comparisons) • Higher order aberration progression index correlated with OSDI overall score/ocular symptoms and OSDI vision-related activities of daily living subscores • OSDI overall score negatively correlated with TBUT/Schirmer's test
Deschamps et al 2013[21]	France	• Prospective case-control study to assess visual performance while driving	• OSDI	DED (n=20), controls (n=20)	• Significantly higher OSDI overall score/subscores in patients with DED versus controls ($P<.01$ for all comparisons)
Jacobi et al 2011[23]	Germany	• Prospective nonrandomized single-center study evaluating tear film osmolarity using electrical impedance technology	• OSDI	DED (n=133), controls (n=95)	• Significantly higher OSDI score in patients with DED versus controls ($P<.05$)
Iannuccelli et al 201[27]	Italy	• Cross-sectional survey to assess fibromyalgia symptoms in SS and SLE	• Fatigue VAS • Pain VAS • HAQ • ZSDS • ZSAS	Primary SS (n=50), SLE (n=50)	• No significant differences in fatigue and pain VAS scores, HAQ, ZSDS, and ZSAS (SLE vs primary SS) • Mean (±SD) ZSDS scores: 48.24 ± 17.20 versus 49.46 ± 13.63 (SLE vs primary SS) • Mean (±SD) ZSAS scores: 50.04 ± 13.48 versus 48.86 ± 11.16 (SLE vs primary SS)
Belenguer et al 2005[24]	Spain	• Survey to evaluate HRQoL in primary SS and correlation with clinical features • Patients seen consecutively in outpatient clinic	• SF-36	Primary SS (n=110), controls (n=9,151)	• All SF-36 scale scores significantly lower for patients with primary SS versus controls (role-physical, role-emotional, vitality, mental health, social functioning, bodily pain, physical functioning, and general health; $P<.001$ for all comparisons)
García-Catalán et al 2009[22]	Spain	• Cross-sectional, case-control study evaluating correlations between HRQoL and clinical signs	• OSDI • VFQ-25	DED (n=19), controls (n=21)	• OSDI total score significantly higher ($P<.001$) and VFQ-25 total score significantly lower ($P=.006$) for patients with DED versus controls

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Table 3. Literature identified on DED-related HRQoL *(continued from previous page)*

Reference	Country	Methods	HRQoL instruments used	Study population (n)	Key findings
					• In patients with DED, significant correlations ($P<.05$) for: - OSDI with VFQ-25 total score ($r=-0.62$) - TBUT with corneal staining ($r=-0.50$) and Schirmer's test (r=0.66) - BUT with OSDI total score, OSDI symptoms, and OSDI triggers ($r=-0.56$, -0.56, and -0.60, respectively) - Corneal staining with OSDI total score and OSDI symptoms ($r=0.55$ and 0.54, respectively) - BUT with VFQ-25 total score, VFQ-25 ocular pain, mental function, and role function ($r=0.56$, 0.51, 0.63, and 0.56, respectively) - Corneal staining with VFQ-25 total score, VFQ-25 ocular pain, and near vision ($r=-0.57$, -0.49, and -0.62, respectively)
Bowman et al 2004[25]	United Kingdom	• Survey to assess fatigue/discomfort in primary SS, SLE, and RA	• SF-36 • WHOQOL-BREF • Symptoms of fatigue/generalized discomfort	Primary SS (n=137), RA (n=74), SLE (n=66), controls (n=103)	• SF-36 and WHOQOL-BREF scales significantly different ($P<.008$) for all disease groups versus controls • Somatic fatigue in the fatigue/generalized discomfort questionnaire significantly more severe over the previous 2 weeks for all disease groups versus controls ($P<.001$) • Patients with primary SS had significantly impaired mental fatigue versus controls ($P<.001$)
Buchholz et al 2006[19]	United Kingdom	• Utility assessment study evaluating impact of DED • Survey via interactive utility assessment software	• TTO and SG for utility • VFQ-25 • OSDI	DED (N=44), of whom had mild/moderate DED (n=24), severe DED (n=20)	• Utilities for DED were in the range of conditions accepted as lowering health utilities - Utilities for severe DED were similar to those reported for severe angina, dialysis, or disabling hip fracture

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Table 3. Literature identified on DED-related HRQoL *(continued from previous page)*

Reference	Country	Methods	HRQoL instruments used	Study population (n)	Key findings
					• Patient-assessed severity correlated with VFQ-25 scores (P=.0016) and OSDI scores (P=.0005) • Statistically significant differences in mean VFQ-25 score (self-rated mild/moderate DED [78.1] versus severe DED [64.5]; P=.005) • Mean utilities for scenarios of DED severity levels slightly higher for mild to moderate versus severe DED (0.72 vs 0.61)
Hackett et al 2012[26]	United Kingdom	• Case-control study to assess function in primary SS and relationship with disease activity, symptoms, and HRQoL	• HAQ • Profile of fatigue • Pain, VAS • HADS • ESSPRI • ESSDAI • EQ-5D • ESS	Primary SS (n=69), controls (n=69)	• Significantly greater functional impairment across all activity domains (mean ± SD improved HAQ total scores, primary SS vs controls: 24 ± 25 vs 9 ± 19; P=.0002) • Primary SS: functional impairment significantly associated with physical fatigue (P<.0001), pain (VAS; P<.0001), depression (HADS; P<.0001), total symptom burden (ESSPRI; P<.0001), systemic disease activity (ESSDAI; P=.001), quality of life (EQ-5D VAS and EQ-5D TTO; P<.0001 for each), daytime somnolence (ESS; P=.02), anxiety score (HADS; P=.03)
Rostron et al 2002[28]	United Kingdom	• Cross-sectional study comparing health status of patients with primary SS and xerostomia	• SF-36	Primary SS (n=43), patients with non-SS reporting xerostomia (n=40)	• Lower mean SF-36 scores across all eight scales (primary SS vs normative community data)
Stevenson et al 2004[29]	United Kingdom	• Cross-sectional study assessing anxiety/depression in primary SS	• HADS	Primary SS (n=40), controls (n=40)	• Significantly higher mean (SD) scores for depression: primary SS, 6 (4.5); controls, 3.7 (2.9); standardized mean difference (95% CI): 0.600 (0.15−1.05) • No significant difference in mean scores for anxiety (primary SS vs controls)

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Table 3. Literature identified on DED-related HRQoL *(continued from previous page)*

Reference	Country	Methods	HRQoL instruments used	Study population (n)	Key findings
North America					
Abetz et al 2011[35]	United States	• Validation study of IDEEL • Differences between severity evaluated by recruited diagnosis (non-SS DED, SS, control), clinician report (mild, moderate, severe symptoms), and patient report (no DED, very mild/mild, very severe/severe)	• IDEEL • SF-36 • EQ-5D	Non-SS DED (n=130), SS (n=32), controls (n=48)	• IDEEL: significant ($P<.0001$) differences in all mean dimension scores (except satisfaction with treatment effectiveness) for different severity levels across the three severity criteria (recruited diagnosis, clinician report, or patient report) • SF-36: significant ($P<.0001$) differences in PCS scores between different severity levels across the three severity criteria. Differences across severity levels for MCS scores were only significant for clinician report and patient report • EQ-5D: significant ($P<.0001$) differences in mean dimension scores for the different severity levels across the three severity criteria
Fairchild et al 2008[34]	United States	• Prospective randomized study to assess utility of IDEEL-SB to discriminate self-assessed DED severity and changes in condition after treatment (lubricating eye drops)	• IDEEL-SB	DED (N=74)	• At baseline, mean (± SD) IDEEL-SB score: mild, 40.0 (± 7.5); moderate, 50.6 (± 11.0); severe, 64.3 (± 8.0) • Mean IDEEL-SB score significantly correlated with self-reported severity ($P=.001$)
Mertzanis et al 2005[37]	United States	• Part of IDEEL validation study • The relative burden of DED was compared using SF-36 responses from patients with DED and controls against US norms (general population from the SF-36 Health Survey manual and interpretation guide[55])	• SF-36	Non-SS DED (n=130), SS (n=32), controls (n=48)	• Patients with non-SS DED: lower SF-36 scores versus adjusted norm for role-physical (ES, −0.07), bodily pain (ES, −0.08), vitality (ES, −0.11); higher physical functioning (ES, 0.09), general health (ES, 0.13), social functioning (ES, 0.19), role-emotional (ES, 0.07), and mental health (ES, 0.06) versus adjusted norm • Patients with SS: all SF-36 scale scores, except mental health (ES, 0.12), lower versus adjusted norm (ES range, −0.16 to −0.99) • Clinician-reported severity levels versus norms: - Patients with mild DED: lower scores for role-physical, bodily

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Table 3. Literature identified on DED-related HRQoL *(continued from previous page)*

Reference	Country	Methods	HRQoL instruments used	Study population (n)	Key findings
					pain, vitality, and general health (ES range, −0.01 to −0.17); higher scores for physical functioning, social functioning, role-emotional, and mental health (ES range, 0.03 −0.13) - Moderate DED: lower scores on role-physical (ES, −0.32), bodily pain (ES, −0.21), vitality (ES, −0.42), role-emotional (ES, −0.22), and mental health (ES, −0.19) - Severe DED: lower scores versus adjusted norm across all domains (ES range, −0.38 to −0.91), with the exception of role-emotional (ES, −0.13) and mental health (ES, −0.23) • Patients with non-SS DED and SS: when DED severity is assessed by clinician, mental health is unaffected by DED symptoms, but when self-reported symptoms are severe, there is a negative effect on mental health (ES, −0.14)
Miljanovic et al 2007[39]	United States	• Cross-sectional study to evaluate impact of DED on vision-related QoL • Participants from Women's Health and Physicians' Health studies	• 11-item questionnaire assessing vision-related QoL	DED (n=190), controls (n=399)	• Patients with DED significantly more likely to report problems with reading (OR, 3.64; 95% CI, 2.45−5.40; $P<.001$), doing professional work (OR, 3.49; 95% CI, 1.72−7.09; $P=0.001$), using a computer (OR, 3.37; 95% CI, 2.11 −5.38; $P<.001$), watching television (OR, 2.84; 95% CI, 1.05−7.74; $P=.04$), daytime driving (OR, 2.80; 95% CI, 1.58 −4.96; $P<.001$), or nighttime driving (OR, 2.20; 95% CI, 1.48−3.28; $P<.001$)
Nichols et al 2002[33]	United States	• Validation study of VFQ-25 • Recruited from university-based optometry practice	• VFQ-25	DED (N=75)	• Mean (± SD) ocular pain subscale score significantly different between moderate to severe DED (60.8 ± 14.1 points) and milder DED (71.8 ± 19.2 points; visit 1: Wilcoxon rank-sum, $P=.009$)

Table 3. continues on the following page

Table 3. Literature identified on DED-related HRQoL *(continued from previous page)*

Reference	Country	Methods	HRQoL instruments used	Study population (n)	Key findings
Rajagopalan et al 2005[36]	United States and Canada	• Validation study of SF-36, EQ-5D, and IDEEL • Severity was assessed based on diagnosis (non-SS DED, SS, control), patient report (none, very mild, mild, moderate, severe, extremely severe) and clinician report (none, mild, moderate, severe) • Assessment of patient-reported severity provided by DEQ	• SF-36 • EQ-5D • IDEEL	Non-SS DED (n=130), SS (n=32), controls (n=48)	• Significantly different ($P<.05$) SF-36 scores between various severity levels, except for role-emotional by patients' recruited diagnosis and self-rated severity; physical functioning by clinician-rated severity and self-rated severity; and bodily pain by clinician-rated severity • Significant differences in EQ-5D QoL scores ($P<.05$) and VAS ($P<.0001$) across all severity measures • For recruited diagnosis and clinician-rated severity, significant differences in IDEEL scores between different levels of severity ($P<.0001$) in all scores except treatment satisfaction
Schiffman et al 2003[38]	United States	• Survey to determine utilities for DED • Patients with mild, moderate, or severe DED	• TTO dry eye utilities • SF-36 • VFQ-25	DED (N=40)	• Mean TTO utilities for moderate (0.78) and severe DED (0.72) were similar to historical reports for moderate (0.75) and more severe (Class III/IV) angina (0.71), respectively • Significant associations were seen with the SF-36 physical functioning, role-physical, bodily pain, and vitality subscales, and the SF-36 PCS score (all $P\leq.045$); and with the VFQ-25 composite score ($P=.037$)
Sullivan et al 200[40]	United States	• Cross-sectional study to evaluate economic and QoL impact of SS in women	• DEDIQ	Primary/secondary SS (N=45)	• DED symptoms: - Affected lifestyle and leisure activities in ≈60% of patients - Interfered with effectiveness at work in 37.5% of patients
Asia					
Mizuno et al 2010[41]	Japan	• Multicenter prospective cohort study to assess impact of DED on QoL and associations between symptoms and ocular surface findings	• VFQ-25 • SF-8	DED (N=158), of whom had SS (n=60), non-SS DED (n=98)	• Some patients with DED recorded extremely low VFQ-25 scores • Lower SF-8 PCS and MCS scores versus healthy individuals - Differences between patients with SS and non-SS DED not significantly different

Table 3. continues on the following page

Table 3. Literature identified on DED-related HRQoL *(continued from previous page)*

Reference	Country	Methods	HRQoL instruments used	Study population (n)	Key findings
					• Lower SF-8 PCS and MCS scores for DED versus healthy individuals • Low association between fluorescein staining score and general vision subscale of VFQ-25 ($r=-0.176$; $P<.05$). However, no associations between all other ocular surface findings and VFQ-25/SF-8

CI, confidence interval; DED, dry eye disease; DEDIQ, Dry Eye Disease Impact Questionnaire; DEQ, Dry Eye Questionnaire; EQ-5D, EuroQol 5-Dimensions; ES, effect size; ESS, Epworth Sleepiness Scale; ESSDAI, European League Against Rheumatism Sjögren's Syndrome Disease Activity Index; ESSPRI, European League Against Rheumatism Sjögren's Syndrome Patient Reported-Index; HADS, Hospital Anxiety and Depression Scale; HAQ, Health Assessment Questionnaire; HRQoL, health-related quality of life; IDEEL, Impact of Dry Eye on Everyday Life questionnaire; IDEEL-SB; Impact of Dry Eye on Everyday Life questionnaire-symptom bother; MCS, mental component summary; OR, odds ratio; OSDI, Ocular Surface Disease Index; PCS, physical component summary; QoL, quality of life; RA, rheumatoid arthritis; SF-8, 8-item Short-Form Health Survey; SF-36, 36-item Short-Form Health Survey; SG, standard gamble; SLE, systemic lupus erythematosus; SS, Sjögren's syndrome; TBUT, tear film breakup time; TTO, time trade-off; VAS, visual analog scale; VFQ 25, 25-item Visual Function Questionnaire; WHOQOL-BREF, World Health Organization Quality of Life-BREF scale; ZSAS, Zung Self-Rating Anxiety Scale; ZSDS, Zung Self-Rating Depression Scale.

US study, data for patients with DED that initiated treatment with topical cyclosporine (Restasis®, Allergan, Inc., Irvine, CA) or punctal plugs were analyzed from a research database containing health plan enrollment, medical claims, and pharmacy claims data (extracted for 2004–2005).[12] Of the commercial health plan enrollees who met inclusion criteria, 9,065 had received topical cyclosporine and 8,758 had received punctal plugs. The annual total mean health plan costs were US $3.05 million for the topical cyclosporine cohort (US $336 per patient) and US $3.28 million for the punctal plug cohort (US $2.24 million [US $256 per patient] for initial punctal plug procedures and an additional US $1.04 million [US $307 per patient] for subsequent procedures during the 365-day follow-up period).

c. Asia

The literature on direct costs in Asia is more limited than in Europe and the United States, with no studies from China and only one small cohort study in Japan. In this study, Mizuno et al evaluated direct DED-related costs for 2008 among 118 patients with DED using outpatient medical records and survey questionnaires.[6] Direct costs were composed of medical and drug costs, including costs related to artificial tear use and punctal plugs. Direct annual costs per patient were estimated at ¥52,467 (US $530), comprising clinical costs of ¥16,318 (US $165), drug costs of ¥32,000 (US $323), and costs for punctal plugs of ¥4149 (US $42).

2. Treatment Utilization and Costs

a. Europe

In the study by Clegg et al, the cost of prescription drugs varied across France, Germany, Italy, Spain, and the United Kingdom, with the cost per 1,000 patients with DED ranging from US $22,000 in France to US $535,000 in the United Kingdom for 2003 to 2004.[9] It should be noted when comparing these data with other regions that topical cyclosporine (which was associated with an increase in prescription costs after its introduction in the United States[13]) is not currently available in Europe.

b. United States

Of the US literature identified, two studies examined overall DED-related prescription costs.[13,14] A retrospective study by Galor et al reviewed the expenditures of 147 participants in the Medical Expenditure Panel Survey (a subsample of the US National Health Interview Survey). This study showed that the total number of prescriptions for treatments for DED increased substantially after the introduction of topical cyclosporine in 2003,[13] with the cost associated with DED prescription medications increasing from a mean US $55 per patient per year in 2001-2002 to US $299 per patient per year in 2005-2006. The Medical Expenditure Panel Survey also showed that mean annual DED medication expenditure per patient for females was twice that of males (US $244 vs US $122; $P<.0001$), while age was not found to be a significant factor after controlling for other covariates. In the second study, which was

published in 2003, the annual cost of using palliative medications, punctal plugs, and surgery to manage and treat DED was estimated to be US $357,050 for an organization covering 500,000 lives.[14] Three additional studies investigated the cost and cost-effectiveness of treatment with topical cyclosporine.[5,12,15] Notable among these was the claims analysis by Fiscella et al, which reported mean treatment cost per patient at US $336 for topical cyclosporine and US $375 for punctal plug procedures in the 1-year follow-up period (2004−2005).[12] One further study reported unit costs of medications, surgical procedures, and health care professional visits for patients with DED in 2003.[7]

c. *Asia*

As reviewed above, Mizuno et al estimated that in Japan, the total annual direct drug cost per patient was ¥32,000 (US $323), and the annual cost of punctal plugs was ¥4,149 (US $42) in 2008.[6] It is worth noting that these costs were estimated before diquafosol ophthalmic solution (Diquas™, Santen Pharmaceutical Co., Ltd., Osaka, Japan) became available in Japan in 2010, so drug costs might be expected to be higher after this date. Topical cyclosporine also was unavailable in Japan at the time of the study. Our literature search did not identify any studies reporting treatment utlization or costs in China.

3. Productivity Loss and Related Indirect Costs

a. *Europe*

No literature was identified reporting on DED-related productivity loss or indirect costs in Europe.

b. *United States*

We identified four studies from the United States that examined productivity loss and indirect costs related to DED.[8,14,16,17] In the study by Yu et al, the average annual indirect DED cost to society for 2008 was estimated at US $11,302 per patient owing to reduced productivity.[8] The authors estimated that this corresponds to a total burden of productivity loss and related indirect cost of US $55.4 billion in the United States. The study also measured reductions in productivity owing to absenteeism (the loss of working time owing to absence or leaving early) and presenteeism (impairment at work/reduced on-the-job effectiveness) using the Work Productivity and Activity Impairment Questionnaire. The level of both presenteeism and absenteeism differed according to the severity of DED: the number of days lost per year owing to affected performance was estimated at 91, 94.9, and 128.2 days for mild, moderate, and severe DED, respectively, and the estimated direct number of work days lost per year was 8.4, 3.7, and 14.2 days, respectively.[8] In a cross-sectional, web-based survey that also used the Work Productivity and Activity Impairment Questionnaire, reduced productivity while at work was reported at all levels of disease severity (mild, moderate, and severe DED).[17] Further evidence of the negative impact of DED on work productivity was provided by a study published in 2000, in which patients with DED reported 184 work days of reduced productivity per year (estimated at US $5,362 per individual).[14] Another study reported that a sample of SS patients with DED worked 208 days of the year with DED symptoms and were absent from work for 5 days owing to their DED symptoms/treatment.[16]

c. *Asia*

Only one study reporting the impact of DED on work productivity was identified from Japan, with no studies from China. In the Japanese study, the impact of DED on the work productivity of 355 office workers was evaluated using the Japanese version of the Work Limitations Questionnaire (cost extracted 2011).[18] Participants were grouped into four categories according to diagnosis by an ophthalmologist and subjective symptoms. These were definite DED (diagnosis and symptoms), marginal DED (diagnosis but no symptoms), self-reported DED (symptoms but no diagnosis), and controls (no diagnosis or symptoms). Productivity was significantly lower in participants with self-reported DED compared with controls ($P<.05$), with the annual cost of work productivity loss associated with DED estimated at US $741 (¥59,758) per patient.

In addition, work performance in the self-reported DED group was significantly lower compared with controls ($P<.05$; work performance loss: self-reported DED, 6.06%, controls, 4.27%).

B. HRQoL Burden of DED

The studies meeting our selection criteria for inclusion in the systematic review quantitatively and qualitatively assessed HRQoL in patients with DED using a variety of instruments, including DED-specific, vision-specific, generic, work productivity, and anxiety/depression instruments. These instruments are summarized in Table 4 for reference.

1. Europe

Overall, we identified 11 studies in Europe that reported HRQoL measures either in patients diagnosed with DED[19-23] or those with primary SS.[24-29] The studies conducted in SS patients did not distinguish the burden attributable to DED from that due to other aspects of SS. We included these studies on the basis that DED is a key clinical manifestation of SS.[2,30] However, it should be noted that the DED in SS is generally more severe than non-SS DED[31] and therefore the burden is likely to be greater. All 11 studies demonstrated a significant negative effect of DED/primary SS on at least some aspects of HRQoL.

The most frequently used DED- or vision-specific instrument was the Ocular Surface Disease Index (**OSDI**), which is designed to assess DED-related HRQoL across three subscales: ocular symptoms, vision-related activities of daily living, and environmental triggers. A cross-sectional case-control study reported significantly higher (worse) OSDI total scores and significantly lower (worse) 25-item Visual Function Questionnaire (**VFQ-25**) scores in patients with DED compared with controls.[22] Three prospective studies also reported significantly worse OSDI overall scores for the

Table 4. Instruments used to assess HRQoL/symptoms in DED

Instrument	Summary
DED and vision specific	
DEDIQ[15,54]	33 items that evaluate DED symptoms and consequent actions taken by patients
DEQ 2001[56]	21 items that evaluate the prevalence, frequency, diurnal severity, and intrusiveness of DED symptoms (1−5 scale; 0=best, 100=worst)
ESSDAI[57]	Clinical index of disease activity measurement based on the assessment of 12 organ domains (constitutional, lymphadenopathy, glandular, articular, cutaneous, pulmonary, renal, muscular, peripheral nervous system, central nervous system, hematological, and biological; 0−123 scale; higher scores indicate worse disease activity)
ESSPRI[58]	Index of the mean score of key primary SS symptoms: dryness, pain, and fatigue (0−10 scale; higher scores asociated with worse disease activity)
IDEEL[36]	57 questions comprising three modules: dry eye symptom-related bother, impact on daily life, and treatment satisfaction (0−100 scale; higher scores indicate better QoL, worse symptoms, and better treatment satisfaction)
OSDI[59]	Patient-reported index consisting of 12 questions covering three domains: ocular symptoms, vision-related function, and environmental triggers (0−100 scale; 0=no disability, 100=complete disability)
VAS[2]	Psychometric response scale used to grade a specific disease symptom or attitude, e.g., ocular discomfort, dryness (0 −100 mm scale; 100 mm maximum)
VFQ-25[60]	25-item version of the 51-item NEI-VFQ. Consists of five nonvisual domains (general health, mental health, dependency, social function, role limitations) and seven visual domains (general vision, distance vision, peripheral vision, driving, near vision, color vision, and ocular pain; 0−100 scale; 0=worst, 100=best)
Generic	
HAQ[61]	Eight domains of physical function; ability to perform daily activities is rated on a five-point scale (0=without difficulty; 4=unable to do)
EQ-5D[62]	Five measures of health outcome are assessed (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression; 0−100 scale; higher scores indicate better overall health status)
ESS[63]	Index that measures average daytime sleepiness (0−24 scale; score $\geq$10 indicates excessive level of daytime sleepiness)
SF-36[64]	36 questions yield a profile of two health component summary measures (PCS and MCS) and eight health domain scales: role-physical, role-emotional, vitality, mental health, social functioning, bodily pain, physical functioning, and general health (0−100 scale; higher scores indicate better self-perceived health)
Utility assessment questionnaire[38]	Tool for quantifying the relative impact of a specific disease on HRQoL. Utility values can be measured by methods such as SG or TTO (adjusted to scores from 1.0=perfect health to 0.0=death; scores closer to 1.0 indicate better QoL)

Table 4. continues on the following page

Table 4. Instruments used to assess HRQoL/symptoms in DED *(continued from previous page)*

Instrument	Summary
WHOQOL-BREF[65]	Cross-cultural measurement tool; comprises 26 items that address four domains: physical health, psychological health, social relationships, and environment (higher scores indicate higher QoL)
Anxiety and depression	
HADS[66]	14-item scale that determines levels of anxiety and depression in people with physical health problems (0–42 scale; higher scores indicate worse mental health)
ZSAS[67]	20-item self-report assessment survey that measures anxiety levels (score, 20–80; normal range, 20–44)
ZSDS[68]	20-item self-report assessment survey that measures depressed status (score, 25–100; normal range, 25–49)

DED, dry eye disease; DEDIQ, Dry Eye Disease Impact Questionnaire; DEQ, Dry Eye Questionnaire; EQ-5D, EuroQol 5-Dimensions; ESS, Epworth Sleepiness Scale; ESSDAI, European League Against Rheumatism Sjögren's Syndrome Disease Activity Index; ESSPRI, European League Against Rheumatism Sjögren's Syndrome Patient-Reported Index; HADS, Hospital Anxiety and Depression Scale; HAQ, Health Assessment Questionnaire; HRQoL, health-related quality of life; IDEEL, Impact of Dry Eye on Everyday Life questionnaire; MCS, mental component summary; NEI-VFQ, National Eye Institute Visual Function Questionnaire; OSDI, Ocular Surface Disease Index; PCS, physical component summary; QoL, quality of life; SF-36, 36-item Short-Form Health Survey; SG, standard gamble; SS, Sjögren's syndrome; TTO, time trade-off; VAS, visual analog scale; VFQ-25, 25-item Visual Function Questionnaire; WHOQOL-BREF, World Health Organization Quality of Life-BREF scale; ZSAS, Zung Self-Rating Anxiety Scale; ZSDS, Zung Self-Rating Depression Scale.

population of patients with DED compared with controls.[20-23] In two of these studies, results were given for individual OSDI subscales, all of which were shown to be significantly worse than controls.[20,21] A further study that included the OSDI reported correlation between patient-assessed severity and OSDI scores (P=.0005).[19] The primary aim of this study was to assess utility values associated with DED; results showed that severe dry eye utilities were comparable with those reported for dialysis and severe angina. Overall ocular health also was shown to be lower in patients who self-rated themselves as severe compared with those who self-rated themselves as mild/moderate according to VFQ-25 scores.

Among the generic HRQoL instruments, the most frequently used was the 36-item Short-Form Health Survey (**SF-36**) questionnaire, which assesses various aspects of HRQoL (role-physical, role-emotional, vitality, mental health, social functioning, bodily pain, physical functioning, and general health). Two studies reported lower (worse) scores across all eight SF-36 scales in patients with primary SS compared with population-based control reference values[24] or normative community data.[28] A third UK survey reported that patients with primary SS had significantly worse SF-36 and World Health Organization Quality of Life-BREF scale scores compared with controls.[25]

In a UK study that evaluated patients with primary SS using the Health Assessment Questionnaire (**HAQ**), greater functional impairment (higher HAQ scores) in patients with primary SS versus controls was reported across all domains of activity (P=.0002 for HAQ total scores).[26] Functional impairment also was found to be significantly associated with the following clinical features of primary SS: fatigue, pain, overall symptom burden, systemic disease activity, dryness, depression, and HRQoL (all P<.0001).

Two studies in Europe used anxiety/depression instruments to assess the impact of primary SS.[27,29] One study reported that the mean Hospital Anxiety and Depression Scale score for depression in patients with primary SS was significantly higher (worse) compared with controls, although that there was no significant difference in scores for anxiety.[29] A second study from Italy reported that patients with primary SS had similar scores on the Zung Self-rating Anxiety/Depression Scales (corresponding to borderline depression/anxiety) compared with those in patients with systemic lupus erythematosus.[27]

2. United States

We identified eight studies in the United States that assessed the impact of DED on HRQoL, all of which demonstrated a significant negative effect of DED on some aspects of HRQoL.

Five US studies evaluated HRQoL measures according to DED severity.[32-36] In a validation study of VFQ-25, in which DED severity was classified according to the European criteria for keratoconjunctivitis sicca, a significantly lower (worse) mean ocular pain subscale score was reported for patients with moderate to severe DED compared with patients with milder DED.[33] A second US study assessed the relative burden of DED in patients with non-SS DED and SS versus a US normative sample by recruited severity (control, non-SS DED, SS) based on previous diagnosis, patient self-report (none, very mild/mild, moderate, severe/

extremely severe), and clinician report (none, mild, moderate, severe).[37] DED consistently caused bodily pain and decreased role-physical, vitality, and general health scores on the SF-36 subscales, but the impact was only clinically significant (effect size, <0.2) when DED symptoms were reported as moderate or severe. Impairments in physical and social functioning were generally greater for patients with SS compared with those with non-SS DED. In addition, mental health in patients with non-SS DED and SS was unaffected by DED symptoms when DED severity was assessed by the clinician. However, in patients who self-reported their symptoms as severe, a negative effect was reported on mental health (effect size, −0.14).

Further evidence relating to the effect of DED severity on HRQoL is provided by three studies that used the DED-specific Impact of Dry Eye on Everyday Life (**IDEEL**) instrument. This instrument consists of 57 questions covering three domains: dry eye symptom bother, impact on daily life (including daily activities, emotional impact, and impact on work), and treatment satisfaction. In a prospective clinical trial, the mean IDEEL-symptom bother score at baseline correlated with self-assessed DED severity.[34] In two IDEEL validation studies in which DED severity was evaluated according to diagnosis (non-SS DED, SS, control), patient report (none, very mild, mild, moderate, severe, extremely severe), and clinician report (none, mild, moderate, severe), significant differences between severity levels were observed with most IDEEL, SF-36, and EuroQol 5-Dimension scores.[35,36]

A utility assessment study conducted in patients with mild, moderate, or severe DED assessed the impact of DED on HRQoL using the time trade-off method. The results from this study suggest that the impact of moderate to severe DED on patients' HRQoL is similar to that of moderate to severe angina and that the impact of severe DED is similar to severe angina.[38] Two further US studies demonstrated that DED has a negative impact on activities of daily living.[39,40] In one of these, subsets of participants from the Women's Health and Physicians' Health studies were sent an 11-item questionnaire that included questions on the impact of DED on QoL. The results indicate that patients with DED were approximately three times more likely to have problems with reading, engaging in professional work, using a computer, watching television, or driving.[39] A second study that used the Dry Eye Disease Impact Questionnaire to survey 45 women with primary or secondary SS demonstrated that DED has a negative effect on lifestyle and leisure activities as well as effectiveness at work.[40]

3. Asia

The literature from Asia on the impact of DED on HRQoL is limited, with our search identifying no studies from China, and only one multicenter study from Japan. This study reported that some patients with DED had extremely low scores (poor QoL) on the Japanese version of the VFQ-25.[41] In addition, the physical component summary and mental component summary on the 8-item Short-Form Health Survey were lower (worse) than those of healthy individuals. However, the differences between patients with SS and non-SS DED were not significantly different.

IV. DISCUSSION

DED is a chronic and often under-recognized ocular condition for which the economic and HRQoL burden can be substantial. This systematic review provides a comprehensive assessment of the available literature on the economic and humanistic burden of DED in countries across Europe, North America, and Asia.

Overall, the literature search identified only 12 and 20 articles fulfilling study criteria on the economic and HRQoL burden of DED, respectively. These numbers highlight the need for additional research on the burden of DED. Furthermore, most of the economic data were based on costs extracted before 2008, indicating that, in particular, up-to-date estimates of health care resource utilization and costs associated with DED are needed. The majority of economic data were from the United States (nine of 12 articles), and HRQoL data were predominantly from Europe (11 articles) and the United States (eight articles). Our literature search identified only three studies from Japan on the economic and humanistic burden of DED, and no studies from China. This is a major gap in research, particularly as the prevalence of DED in Asia may be relatively high compared with Western countries.[42,43]

Despite the limitations of the published evidence, the available literature suggests that DED has a substantial economic burden, with indirect costs making up the largest proportion of the overall cost owing to a substantial loss of work productivity. In the United States, DED is estimated to cost US $3.84 billion from the payer's perspective and as much as US $55.4 billion to society.[8] However, the true cost of DED to society may be higher, given the widespread use of over-the-counter artificial tears by individuals with DED symptoms. Only four articles from our literature search took account of the cost of over-the-counter preparations. Of these, Brown et al[44] gave the annual cost of artificial tears as US $96 per patient. In a review article that did not meet our search criteria, Gayton et al estimated that in the United States, 7 to 10 million people spend an average US $320 per year on artificial tears.[45]

While DED costs vary between countries, the results of the economic burden of DED across regions are very broadly comparable. For example, annual direct cost per patient, averaged across France, Germany, Italy, Spain, and the United Kingdom, is estimated at US $664,[9] US $783 in the United States,[8] and US $530 in Japan.[6] Drug costs also were found to be comparable across regions (Europe, US $218[9]; United States, US $299[13]; Japan, US $323[6]). However, the cost of DED owing to loss of productivity was estimated to be higher in the United States compared with Japan (US $5,362 vs $741 per patient). Given the higher prevalence of DED in women compared with men,[11,46] this may reflect the lower female employment rates in Japan compared with the United States, with approximately 70% of Japanese

women leaving the workforce after giving birth to their first child compared with approximately one-third in the United States.[47] Work productivity costs were not available for Europe.

The available evidence suggests that DED has an adverse effect on overall HRQoL, function, activities of daily living, and work productivity across the countries examined. A number of studies also indicated that the HRQoL burden increases with the severity of disease. Indeed, results from two utility assessment studies showed that utilities for severe DED are similar to those reported for severe angina.[19,38] Given the demonstrable effect of DED on HRQoL, we believe that the evaluation of HRQoL measures during assessment in the clinic and during the evaluation of new treatments for DED should be undertaken routinely in order to fully elucidate disease severity and impact.

The evidence for the impact of DED on mental health is more limited, with only two studies in Europe using instruments designed to address this question.[27,29] Unfortunately, these studies were conducted in SS patients and the burden of DED was not separated from other aspects of SS. Results reported from studies outside of this review (as they did not meet the prespecified search criteria) suggest that DED may indeed be associated with depression.[48,49] The possible association of depression with DED is an important consideration for clinicians treating patients with DED, and may be the result of chronic pain and the negative effects of DED on the patient's QoL, function, and ability to perform everyday activities.

An inherent limitation to our systematic review is that there is significant variability in methods/reporting across the studies identified, including the DED identification/categorization methods, patient ages, time of assessments, methods of data collection/reporting, and HRQoL instruments used. This variability limits comparability of identified data. Another limitation of our literature search was that the upper limit of the search was July 2013, so relevant articles after that date would not have been captured. In addition, because a significant number of the articles we reviewed contained data extracted before 2008, estimates of the economic impact and costs for medical treatment and medications for DED are expected to be higher. Older studies might have underestimated the incidence of DED if MGD was not considered part of the definition of DED, as per the 2007 International Dry Eye Workshop (DEWS)[2] and International Workshop on MGD.[50] In addition, it is known that some DED patients with objective evidence of DED may have an absence of specific symptoms.[51,52] This could also lead to an underestimation of DED when classification relies on patient self-report.

V. CONCLUSIONS

Although published data are limited, the available evidence suggests that DED has a substantial negative impact on physical, and potentially psychological, function and QoL, resulting in a large humanistic burden on patients. In addition, DED has a substantial economic burden, with indirect costs making up the largest proportion of the overall cost. Additional data are needed, particularly in Asia, in order to gain a better understanding of the burden of DED and help inform future resource utilization.

ACKNOWLEDGMENTS

The authors thank Nasser Malik, PhD, of Excel Scientific Solutions, who provided medical writing assistance funded by Shire. The authors also would like to thank Wing Yu Tang and Abhijeet Bhanegaonkar for their contribution to the project.

REFERENCES

1. O'Brien PD, Collum LM. Dry eye: diagnosis and current treatment strategies. *Curr Allergy Asthma Rep* 2004;4:314-9
2. (No authors listed). The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye WorkShop (2007) *Ocul Surf* 2007a;5:75-92
3. Shimmura S, Shimazaki J, Tsubota K. Results of a population-based questionnaire on the symptoms and lifestyles associated with dry eye. *Cornea* 1999;18:408-11
4. (No authors listed). The epidemiology of dry eye disease: report of the Epidemiology Subcommittee of the International Dry Eye WorkShop (2007) *Ocul Surf* 2007b;5:93-107
5. Brown GC, Brown MM, Brown HC, et al. Topical cyclosporine (Restasis) cost-utility analysis. *Evidence-Based Ophthalmology* 2009;10:166-7
6. Mizuno Y, Yamada M, Shigeyasu C. Annual direct cost of dry eye in Japan. *Clin Ophthalmol* 2012;6:755-60
7. Reddy P, Grad O, Rajagopalan K. The economic burden of dry eye: a conceptual framework and preliminary assessment. *Cornea* 2004;23:751-61
8. Yu J, Asche CV, Fairchild CJ. The economic burden of dry eye disease in the United States: a decision tree analysis. *Cornea* 2011;30:379-87
9. Clegg JP, Guest JF, Lehman A, Smith AF. The annual cost of dry eye syndrome in France, Germany, Italy, Spain, Sweden and the United Kingdom among patients managed by ophthalmologists. *Ophthalmic Epidemiol* 2006;13:263-74
10. Schaumberg DA, Dana R, Buring JE, Sullivan DA. Prevalence of dry eye disease among US men: estimates from the Physicians' Health Studies. *Arch Ophthalmol* 2009;127:763-8
11. Schaumberg DA, Sullivan DA, Buring JE, Dana MR. Prevalence of dry eye syndrome among US women. *Am J Ophthalmol* 2003;136:318-26
12. Fiscella RG, Lee JT, Walt JG, Killian TD. Utilization characteristics of topical cyclosporine and punctal plugs in a managed care database. *Am J Manag Care* 2008;14:S107-12
13. Galor A, Zheng DD, Arheart KL, et al. Dry eye medication use and expenditures: data from the Medical Expenditure Panel Survey 2001 to 2006. *Cornea* 2012;31:1403-7
14. Dalzell MD. Dry eye: prevalence, utilization, and economic implications. *Manag Care* 2003;12:9-13
15. Cross WD, Lay Jr LF, Walt JG, Kozma CM. Clinical and economic implications of topical cyclosporin A for the treatment of dry eye. *Manag Care Interface* 2002;15:44-9
16. Hirsch JD. Considerations in the pharmacoeconomics of dry eye. *Manag Care* 2003;12:33-8
17. Patel VD, Watanabe JH, Strauss JA, Dubey AT. Work productivity loss in patients with dry eye disease: an online survey. *Curr Med Res Opin* 2011;27:1041-8
18. Yamada M, Mizuno Y, Shigeyasu C. Impact of dry eye on work productivity. *Clinicoecon Outcomes Res* 2012;4:307-12
19. Buchholz P, Steeds CS, Stern LS, et al. Utility assessment to measure the impact of dry eye disease. *Ocul Surf* 2006;4:155-61

20. Denoyer A, Rabut G, Baudouin C. Tear film aberration dynamics and vision-related quality of life in patients with dry eye disease. *Ophthalmology* 2012;119:1811-8
21. Deschamps N, Ricaud X, Rabut G, et al. The impact of dry eye disease on visual performance while driving. *Am J Ophthalmol* 2013;156:184-189.e3
22. García-Catalán MR, Jerez-Olivera E, Benítez-Del-Castillo-Sánchez JM. [Dry eye and quality of life]. *Arch Soc Esp Oftalmol* 2009;84:451-8. Spanish
23. Jacobi C, Jacobi A, Kruse FE, Cursiefen C. Tear film osmolarity measurements in dry eye disease using electrical impedance technology. *Cornea* 2011;30:1289-92
24. Belenguer R, Ramos-Casals M, Brito-Zerón P, et al. Influence of clinical and immunological parameters on the health-related quality of life of patients with primary Sjögren's syndrome. *Clin Exp Rheumatol* 2005;23:351-6
25. Bowman SJ, Booth DA, Platts RG; UK Sjögren's Interest Group. Measurement of fatigue and discomfort in primary Sjögren's syndrome using a new questionnaire tool. *Rheumatology (Oxford* 2004;43:758-64
26. Hackett KL, Newton JL, Frith J, et al. Impaired functional status in primary Sjögren's syndrome. *Arthritis Care Res (Hoboken)* 2012;64:1760-4
27. Iannuccelli C, Spinelli FR, Guzzo MP, et al. Fatigue and widespread pain in systemic lupus erythematosus and Sjögren's syndrome: symptoms of the inflammatory disease or associated fibromyalgia? *Clin Exp Rheumatol* 2012;30:117-21
28. Rostron J, Rogers S, Longman L, et al. Health-related quality of life in patients with primary Sjögren's syndrome and xerostomia: a comparative study. *Gerodontology* 2002;19:53-9
29. Stevenson HA, Jones ME, Rostron JL, et al. UK patients with primary Sjögren's syndrome are at increased risk from clinical depression. *Gerodontology* 2004;21:141-5
30. Mavragani CP, Moutsopoulos HM. Conventional therapy of Sjogren's syndrome. *Clin Rev Allergy Immunol* 2007;32:284-91
31. Pflugfelder SC. Differential diagnosis of dry eye conditions. *Adv Dent Res* 1996;10:9-12
32. Vitali C, Bombardieri S, Moutsopoulos HM, et al; The European Study Group on Diagnostic Criteria for Sjögren's Syndrome. Assessment of the European classification criteria for Sjögren's syndrome in a series of clinically defined cases: results of a prospective multicentre study. *Ann Rheum Dis* 1996;55:116-21
33. Nichols KK, Mitchell GL, Zadnik K. Performance and repeatability of the NEI-VFQ-25 in patients with dry eye. *Cornea* 2002;21:578-83
34. Fairchild CJ, Chalmers RL, Begley CG. Clinically important difference in dry eye: change in IDEEL-symptom bother. *Optom Vis Sci* 2008;85:699-707
35. Abetz L, Rajagopalan K, Mertzanis P, et al. Impact of Dry Eye on Everyday Life (IDEEL) Study Group. Development and validation of the Impact of Dry Eye on Everyday Life (IDEEL) questionnaire, a patient-reported outcomes (PRO) measure for the assessment of the burden of dry eye on patients. *Health Qual Life Outcomes* 2011;9:111
36. Rajagopalan K, Abetz L, Mertzanis P, et al. Comparing the discriminative validity of two generic and one disease-specific health-related quality of life measures in a sample of patients with dry eye. *Value Health* 2005;8:168-74
37. Mertzanis P, Abetz L, Rajagopalan K, et al. The relative burden of dry eye in patients' lives: comparisons to a U.S. normative sample. *Invest Ophthalmol Vis Sci* 2005;46:46-50
38. Schiffman RM, Walt JG, Jacobsen G, et al. Utility assessment among patients with dry eye disease. *Ophthalmology* 2003;110:1412-9
39. Miljanović B, Dana R, Sullivan DA, Schaumberg DA. Impact of dry eye syndrome on vision-related quality of life. *Am J Ophthalmol* 2007;143:409-15
40. Sullivan RM, Cermak JM, Papas AS, et al. Economic and quality of life impact of dry eye symptoms in women with Sjögren's syndrome. *Adv Exp Med Biol* 2002;506:1183-8
41. Mizuno Y, Yamada M, Miyake Y, Dry Eye Survey Group of the National Hospital Organization of Japan. Association between clinical diagnostic tests and health-related quality of life surveys in patients with dry eye syndrome. *Jpn J Ophthalmol* 2010;54:259-65
42. Lin P-Y, Tsai S-Y, Cheng C-Y, et al. Prevalence of dry eye among an elderly Chinese population in Taiwan: the Shihpai Eye Study. *Ophthalmology* 2003;110:1096-101
43. Lee AJ, Lee J, Saw S-M, et al. Prevalence and risk factors associated with dry eye symptoms: a population based study in Indonesia. *Br J Ophthalmol* 2002;86:1347-51
44. Brown MM, Brown GC, Brown HC, et al. Value-based medicine, comparative effectiveness, and cost-effectiveness analysis of topical cyclosporine for the treatment of dry eye syndrome. *Arch Ophthalmol* 2009;127:146-52
45. Gayton JL. Etiology, prevalence, and treatment of dry eye disease. *Clin Ophthalmol* 2009;3:405-12
46. Hashemi H, Khabazkhoob M, Kheirkhah A, et al. Prevalence of dry eye syndrome in an adult population. *Clin Experiment Ophthalmol* 2014;42:242-8
47. Matsui K, Suzuki H, Eoyang C, et al. *Japan: portfolio strategy. Womenomics 3.0: the time is now*. New York, NY, The Goldman Sachs Group, Inc. Available at: http://www.goldmansachs.com/our-thinking/investing-in-women/bios-pdfs/womenomics3_the_time_is_now_pdf.pdf; 2010. Accessed June 17, 2015
48. Kim KW, Han SB, Han ER, et al. Association between depression and dry eye disease in an elderly population. *Invest Ophthalmol Vis Sci* 2011;52:7954-8
49. Labbé A, Wang YX, Jie Y, et al. Dry eye disease, dry eye symptoms and depression: the Beijing Eye Study. *Br J Ophthalmol* 2013;97:1399-403
50. Nichols KK. The international workshop on meibomian gland dysfunction: introduction. *Invest Ophthalmol Vis Sci* 2011;52:1917-21
51. Sullivan BD, Crews LA, Messmer EM, et al. Correlations between commonly used objective signs and symptoms for the diagnosis of dry eye disease: clinical implications. *Acta Ophthalmol* 2014;92:161-6
52. Viso E, Rodriguez-Ares MT, Abelenda D, et al. Prevalence of asymptomatic and symptomatic meibomian gland dysfunction in the general population of Spain. *Invest Ophthalmol Vis Sci* 2012;53:2601-6
53. Lee JT, Teale CW. Development of an economic model to assess costs and outcomes associated with dry eye disease (poster). Poster presented at: 2000 Spring Practice and Research Forum of the American College of Clinical Pharmacy; April 2—5, 2000; Monterey, CA
54. Hirsch J, Kozma C, Woicik A, Reis B. Economic and quality of life impact on dry eye symptoms: a Sjögren's patient survey (abstract). *Invest Ophthalmol Vis Sci* 1998;39. S65. ARVO Abstract
55. Ware JE, Snow KK, Kosinski M, Gandek B. *SF-36 Health Survey: manual and interpretation guide*. Boston, MA, The Health Institute, New England Medical Center, 1993
56. Begley CG, Chalmers RL, Abetz L, et al. The relationship between habitual patient-reported symptoms and clinical signs among patients with dry eye of varying severity. *Invest Ophthalmol Vis Sci* 2003;44:4753-61
57. Seror R, Ravaud P, Bowman SJ, et al; EULAR Sjögren's Task Force. EULAR Sjögren's syndrome disease activity index: development of a consensus systemic disease activity index for primary Sjögren's syndrome. *Ann Rheum Dis* 2010;69:1103-9

58. Seror R, Ravaud P, Mariette X, et al; EULAR Sjögren's Task Force. EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI): development of a consensus patient index for primary Sjögren's syndrome. *Ann Rheum Dis* 2011;70:968-72
59. Schiffman RM, Christianson MD, Jacobsen G, et al. Reliability and validity of the Ocular Surface Disease Index. *Arch Ophthalmol* 2000;118:615-21
60. Mangione CM, Lee PP, Gutierrez PR, et al; National Eye Institute Visual Function Questionnaire Field Test Investigators. Development of the 25-item National Eye Institute Visual Function Questionnaire. *Arch Ophthalmol* 2001;119:1050-8
61. Maska L, Anderson J, Michaud K. Measures of functional status and quality of life in rheumatoid arthritis: Health Assessment Questionnaire Disability Index (HAQ), Modified Health Assessment Questionnaire (MHAQ), Multidimensional Health Assessment Questionnaire (MDHAQ), Health Assessment Questionnaire II (HAQ-II), Improved Health Assessment Questionnaire (Improved HAQ), and Rheumatoid Arthritis Quality of Life (RAQoL). *Arthritis Care Res (Hoboken)* 2011;63(suppl 11):S4-13
62. The EuroQol Group. EuroQol - a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16:199-208
63. Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. *Sleep* 1991;14:540-5
64. McHorney CA, Ware Jr JE, Raczek AE. The MOS 36-item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care* 1993;31:247-63
65. Skevington SM, Lotfy M, O'Connell KA; WHOQOL Group. The World Health Organization's WHOQOL-BREF quality of life assessment: psychometric properties and results of the international field trial. A report from the WHOQOL group. *Qual Life Res* 2004;13:299-310
66. Whelan-Goodinson R, Ponsford J, Schonberger M. Validity of the Hospital Anxiety and Depression Scale to assess depression and anxiety following traumatic brain injury as compared with the Structured Clinical Interview for DSM-IV. *J Affect Disord* 2009;114:94-102
67. Zung WWK. A rating instrument for anxiety disorders. *Psychosomatics* 1971;12:371-9
68. Zung WWK. A self-rating depression scale. *Arch Gen Psychiatry* 1965;12:63-70