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SYSTEMATIC REVIEW

Effect of tiotropium on quality of life in COPD: a systematic review

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) greatly affects quality of life (QoL). Although QoL is a key concern for the patient, primary endpoints in most clinical trials are objective measures of disease progression.

Methods: A systematic review of double-blind randomised controlled trials was undertaken to identify data relating to the effect of tiotropium on QoL in patients with COPD.

Results: A total of 24 publications met the inclusion criteria. Compared with placebo, in the majority of studies tiotropium statistically significantly improved the St George's Respiratory Questionnaire (SGRQ) total score, although improvement beyond the accepted minimum clinically important difference (MCID) of 4 units was only achieved in three studies, all of which were of less than nine months' duration. Tiotropium also statistically significantly improved the Transition Dyspnoea Index (TDI) focal score, equating to clinically meaningful improvements, in almost all the studies that assessed TDI. In general, higher proportions of patients receiving tiotropium achieved clinically meaningful responses. The addition of other therapies (dual therapy, triple therapy) to tiotropium provided benefits that exceeded the SGRQ MCID and provided further benefit with regard to the TDI.

Conclusions: Tiotropium improves QoL for patients with COPD requiring long-acting bronchodilators, with other additional therapies providing further benefits, depending on the population.

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Keywords COPD, tiotropium, quality of life, systematic review, PROMs

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Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory lung disease, mainly related to smoking and characterised by airflow limitation that is not fully reversible.[1,2] The airflow limitation is associated with an abnormal pulmonary inflammatory response to noxious particles or gases.[1] Worldwide, COPD is a major cause of morbidity and premature mortality.[1] The progressive breathlessness, fatigue, impaired exercise capacity and exacerbations greatly affect quality of life (QoL). Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines emphasise that management of stable COPD should address symptoms and improve QoL, and that preventing exacerbations of COPD is important because of their strong impact on patients' QoL and prognosis.[1] Long-acting bronchodilator pharmacotherapy such as long-acting anticholinergics (LAACs) and long-acting β_2-agonists (LABAs) can significantly improve QoL, lung function and exacerbation outcomes. These agents are recommended for regular use (maintenance therapy) in patients with moderate or worse COPD, with the addition of inhaled corticosteroids (ICS) in some patients with severe COPD and repeated exacerbations.[1]

To date, the majority of clinical trials have used objective measures of clinical disease progression as their primary endpoint; patient-reported outcome measures (PROMs) have also been included, but usually only as secondary endpoints. However, QoL is an important concern for both the patient and physician. Being self-reported, QoL outcomes reflect how the patient feels during treatment, and therefore offer crucial insight into patients' perception of treatment success. In fact, the European Agency for the Evaluation of Medicinal Products (EMEA) recommends that symptomatology be a primary endpoint in clinical studies of COPD, preferably using a disease-specific health-related QoL (HRQoL) questionnaire.[3]

The US Food and Drug Administration (FDA) definition of a PROM is a measurement of a patient's health status that comes directly from the patient, without interpretation by a doctor or anyone else.[4] PROM instruments usually consist of questionnaires focusing on several aspects of health (e.g. daily activities, symptoms), often summed to give a total score and including two broad categories: disease-specific instruments (tailored for a specific disease such as COPD) and generic instruments (asking generalised questions). PROM instruments commonly used in trials of COPD include the St George's Respiratory Questionnaire (SGRQ) and the Transition Dyspnoea Index (TDI), both of which can be self-administered. The SGRQ is a 50-item (76 weighted responses) lung-disease specific questionnaire focusing on three domains: symptoms (frequency and severity); activity (activities causing or limited by breathlessness); and impact (social functioning, psychological disturbances resulting from airways disease).[5] The TDI assesses breathlessness.[6,7] Other PROMs used in COPD trials include the Borg Dyspnoea Index (assessing breathlessness)[8] and the Short Form (SF)-36 (assessing general HRQoL).[9] The TDI and Borg Dyspnoea Index are used to measure breathlessness, which is an important measure in overall evaluation of quality of life.

The aim of this study was to review systematically the literature on the effect of the LAAC tiotropium (SPIRIVA®; Boehringer Ingelheim) on HRQoL. The search was limited to double-blind randomised controlled trials (RCTs).

Methods

A literature search was conducted on 25th November 2009 using electronic databases (PubMed, EMBASE, and BIOSIS). Search terms were 'tiotropium OR Spiriva AND quality of life' and 'tiotropium OR Spiriva AND treatment outcome(-s) AND ((CRQ OR SGRQ OR VSRQ OR (chronic OR george(-s) OR virtual simplified) respiratory questionnaire) OR TDI OR transitional dyspn(-ea, -oea) index OR BORG OR (euro qol OR eq) 5d) OR (SF OR short form) 36)'.

The search was limited to clinical trials published in English between 1990 and 2009. Results were reviewed manually for relevance according to the criteria below. Inclusion criteria included double-blind RCTs with a tiotropium arm, in patients with a diagnosis of COPD and a smoking history of ≥10 pack-years. Both placebo- and active-controlled trials were eligible for inclusion if they reported primary QoL data, e.g. SGRQ, TDI, Borg, SF-36, European Quality of Life Questionnaire (EQ-5D), Chronic Respiratory Disease Questionnaire (CRQ), and Visual Simplified Respiratory Questionnaire (VSRQ). Secondary analyses of trials were permitted as long as the data produced were new and not duplicated elsewhere. Abstracts were eligible provided they cited the relevant inclusion criteria, or the name of an eligible trial. Secondary data, such as pooled analysis of previously published trials, and observational and open-label studies were excluded.

Results

Summary of search findings

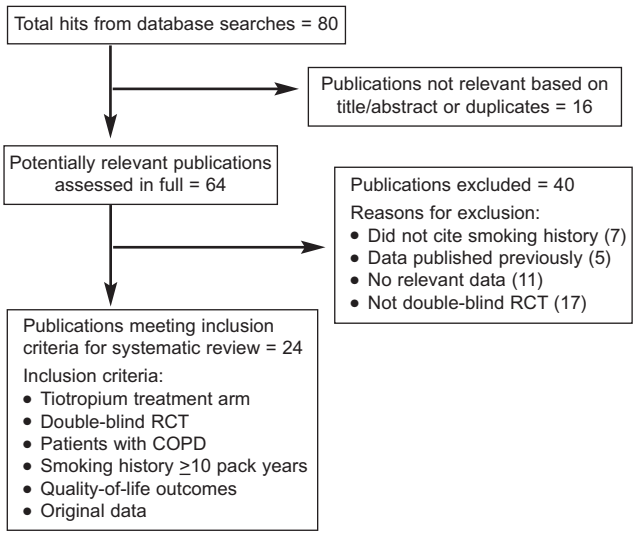
The literature search returned a total of 80 hits. 16 studies were excluded based on the title/abstract and identification of duplicates, while the remaining 64 were reviewed in full and assessed for relevance. Of these, 40 were excluded and 24 were included in the systematic review (see Figure 1).

Of the 40 excluded publications, seven did not cite an eligible smoking history,[10-16] five reported duplicate data published elsewhere,[17-21] 11 reported no relevant data,[22-32] and 17 were not double-blind RCTs.[33-49]

Of the 24 publications that met the inclusion criteria for this systematic review (see Table 1), 16 compared tiotropium with placebo,[50-65] seven compared tiotropium with an active comparator,[66-72] and one compared tiotropium with both placebo and an active comparator.[73]

The QoL outcomes reported in the 24 included publications

Figure 1. Flow diagram of systematic review.



were mostly SGRQ and/or TDI (Tables 2 and 3). Others included the SF-36[51,70] and Borg Dyspnoea Index.[58,65]

Effect of tiotropium versus placebo on quality of life

A total of 17 publications compared tiotropium with placebo on SGRQ (Table 2). The comparable primary data are presented in Table 4. Compared with placebo, a statistically significant improvement in mean SGRQ total score was seen with tiotropium in the 4-year Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT®) trial[60] and other studies lasting six months to one year.[51,54,62,73] Shorter-term studies were less consistent in terms of SGRQ total score; a 12-week study[65] concurred with the significant findings of the longer-term trials, but 25-week studies using concurrent pulmonary rehabilitation[50,52] found no significant difference between tiotropium and placebo. The improvement in mean SGRQ total score did not reach the level of clinically meaningful change (-4 units; Table 4) in the majority of these trials; however, significantly more patients achieved this

Table 1. Details of the included studies.

Citation	Study design	Interventions	Patients	Endpoints
Tiotropium vs placebo				
50	RCT, double-blind, parallel group, 25 weeks	Tiotropium 18 µg vs placebo od; 5 weeks prior to, 8 weeks during, and 12 weeks following pulmonary rehabilitation	234 patients with COPD and smoking history >10 pack-years. Mean BDI 6.6 for both groups	Pulmonary function testing, 6-minute walk test, TDI, and SGRQ
52	RCT, double-blind, parallel group, 25 weeks	Tiotropium 18 µg od vs placebo; 5 weeks prior to, 8 weeks during, and 12 weeks following pulmonary rehabilitation	108 patients with COPD and smoking history >10 pack-years. Mean BDI 5.7 units in both groups	Primary endpoint: treadmill walking endurance time. Others: TDI, SGRQ, and rescue medication use
57	Subgroup analysis of 52		46 patients who completed activity questionnaires. Mean BDI 5.9 both groups	
51	RCT, double-blind, parallel group, 1 year (2 studies)	Tiotropium 18 µg od vs placebo	921 patients with stable COPD and smoking history ≥10 pack-years	Primary outcome: trough FEV_1. Others: TDI, SGRQ, SF-36, medication use
59	Secondary analysis of 51		921 patients stratified as responsive to tiotropium [TIO-R] or poorly responsive [TIO-PR] based on FEV1. Mean BDI 5.77–6.28	
60	RCT, double-blind, parallel group, 4 years (UPLIFT® trial)	Tiotropium 18 µg od vs placebo	5993 patients with COPD with smoking history ≥10 pack-years	Primary endpoint: rate of decline in FEV_1. Secondary endpoints: other lung function, SGRQ, exacerbations, and mortality.
56	Secondary analysis of UPLIFT® trial		5783 patients stratified based on response to acute bronchodilator response	
53	Subgroup analysis of UPLIFT® trial		356 patients who were aged ≤50 years	
55	Subgroup analysis of UPLIFT® trial		2739 patients with moderate COPD (GOLD stage II)	
61	Secondary analysis of UPLIFT® trial		5993 patients stratified based on smoking status	
63	Secondary analysis of UPLIFT® trial		Patients stratified based on concomitant use of LABA (n=2982), ICS (n=2902), or LABA+ICS (n=2260)	
64	Subgroup analysis of UPLIFT® trial		810 patients who were not receiving maintenance drugs at randomisation	
54	RCT, double-blind, parallel group, 48 weeks	Tiotropium 18 µg od vs placebo	913 patients with COPD and smoking history ≥10 pack-years	Primary endpoint: lung function. Others: SGRQ, exacerbations, hospitalisations, rescue medication
58	RCT, double-blind, parallel group, 42 days	Tiotropium 18 µg od vs placebo	261 patients with COPD and smoking history >10 pack-years	Primary endpoint: endurance time. Others: pulmonary function, Borg dyspnoea intensity
62	RCT, double-blind, parallel group, 9 months	Tiotropium 18 µg od vs placebo	554 patients with moderate-to-severe COPD and smoking history >10 pack-years	Primary endpoint: % patients with reduction ≥4 units (SGRQ total score). Others: VSRQ, exacerbations, spirometry
65	RCT, double-blind, parallel group, 12 weeks	Tiotropium 18 µg od vs placebo	100 patients with moderate-to-severe COPD and smoking history ≥10 pack-years. Mean BDI 5.9 both groups	Primary endpoint: change from baseline in trough FVC. Others: spirometry, exercise capacity, TDI, Borg dyspnoea, SGRQ
Tiotropium vs placebo vs active comparator				
73	RCT, double-blind, parallel group, 6 months (2 studies)	Tiotropium 18 µg od plus placebo, salmeterol 50 µg bid plus placebo, or a combination of placebos	1207 patients with COPD and smoking history >10 pack-years	Exacerbations, health resource use, TDI, SGRQ, and spirometry

continued overleaf

Table 1. Details of the included studies continued.

Citation	Study design	Interventions	Patients	Endpoints
Tiotropium vs active comparator				
67	RCT, double-blind, parallel group, 6 weeks (after 7-14-day open-label run-in on tiotropium)	Tiotropium 18 µg od plus formoterol 20 µg bid vs tiotropium 18 µg od plus placebo	155 patients with COPD and smoking history ≥10 pack-years. Mean BDI 5.8–5.92	Primary endpoint: FEV_1 AUC. Others: spirometry, TDI, symptoms, SGRQ, exacerbations, rescue medication use
66	RCT, double-blind, parallel group, 1 year	Tiotropium 18 µg od plus placebo vs tiotropium 18 µg od plus salmeterol 50 µg bid vs tiotropium 18 µg od plus fluticasone-salmeterol 500/50 µg bid	449 patients with moderate or severe COPD and smoking history ≥10 pack-years	Primary endpoint: % patients with exacerbation. Secondary outcomes: number of exacerbations and hospitalisations, SGRQ, TDI, and lung function
68	RCT, double-blind, 14 days each 3-way crossover, with 2 weeks washout between (total duration 13 weeks)	Triple therapy SFC 50/500 µg bid plus tiotropium 18 µg od vs SFC alone vs tiotropium alone	41 patients with COPD and smoking history ≥10 pack-years	Primary endpoint: sGaw AUC. Secondary endpoints: pulmonary function, TDI, rescue medication use
69	RCT, double-blind, parallel group, 6 weeks (after 7–14 day run-in on tiotropium)	Tiotropium monotherapy (tiotropium 18 µg od plus placebo) vs combined therapy (tiotropium 18 µg od plus formoterol 20 µg bid)	130 patients with COPD and smoking history >10 pack-years. BDI 6.3–6.4	Primary endpoint: FEV_1 AUC. Others: spirometry, SGRQ, TDI, symptoms, compliance
70	RCT, double-blind, parallel group, 1 year (2 studies) (3-month partial data was previously published)	Tiotropium 18 µg od vs ipratropium 40 µg qid	535 patients with COPD and smoking history ≥10 pack-years. BDI 7.13 (tiotropium) and 7.41 (ipratropium)	Spirometry, peak expiratory flow rate, rescue medication, TDI, SGRQ, SF-36, exacerbations
71	RCT, double-blind, parallel group, 2 years (after 2-week run-in on steroids plus salmeterol) (INSPIRE trial)	Tiotropium 18 µg od vs SFC 50/500 µg bid	1323 patients with severe COPD, history of exacerbations, and smoking history ≥10 pack-years	Primary endpoint: rate of health care utilisation exacerbations. Secondary endpoints: SGRQ, FEV_1, withdrawal rate, and all-cause mortality
72	RCT, double-blind, parallel group, 12 weeks (after 2-week run in on tiotropium)	Tiotropium monotherapy (tiotropium 18 µg od plus placebo) vs triple therapy (tiotropium 18 µg od plus budesonide/formoterol 320/9 µg bid)	660 patients with severe COPD. and smoking history ≥10 pack-years	Primary endpoint: FEV_1. Others: lung function, SGRQ-C, rescue medication, exacerbations

AUC: Area under curve; bid: Twice daily; BDI: Baseline dyspnoea index; COPD: Chronic obstructive pulmonary disease; FEV_1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; ICS: Inhaled corticosteroids; LABA: Long-acting β-agonist; od: Once daily; PR: pulmonary rehabilitation; qid: four times daily; RCT: Randomised controlled trial; sGaw: specific airways conductance; SF-36: Short form-36; SFC: salmeterol plus fluticasone propionate; SGRQ: St George's Respiratory Questionnaire; SGRQ-C: St George's Respiratory Questionnaire for COPD; TDI: Transitional Dyspnoea Index; TIO-R: Tiotropium-responsive; TIO-PR: Tiotropium-poorly responsive; VSRQ: Visual Simplified Respiratory Questionnaire.

improvement with tiotropium than with placebo.[59,60,62,65,73] The difference in other studies did not reach either statistical or clinical significance[54] or the p value was not reported.[51] This benefit of tiotropium on SGRQ total score was reflected in significant improvements in all three SGRQ domains,[51,62] or two domains (symptoms and impact);[54] the difference in another study did not reach statistical significance.[50]

Although a clinically significant improvement of -4 units in SGRQ total score compared with placebo was not observed in the full cohort in the UPLIFT® trial (range, -2.3 to -3.3 units),[60] it is notable that both statistically and clinically significant changes occurred in the GOLD Stage II patient subgroup (range, -2.7 to -4.0 units),[55] patients not receiving maintenance therapy at baseline (-4.6 units at 4 years),[64] and continuing smokers (-4.6 units at 4 years).[61] In terms of SGRQ domains (where reported), symptom and activity domains were improved in GOLD Stage II patients (up to -4.1 and -4.4 units, respectively)[55] and all three domains (impact, symptom, and activity) improved in continuing smokers (-4.2, -4.7, -5.7 units respectively).[61]

Seven publications compared TDI focal score for tiotropium versus placebo (Table 2). The comparable primary data are presented in Table 4. Both a statistically significant and clinically meaningful improvement (1 unit) in mean TDI focal score for tiotropium over placebo was seen in studies lasting six months[73] and one year.[51] The 25-week studies using concurrent pulmonary rehabilitation were less consistent,[50,52] and the improvement in a 12-week study did not reach statistical significance.[65] The benefit of tiotropium was reflected in the significantly greater number of patients achieving a clinically meaningful improvement (of 1 unit) in TDI focal score.[51,73]

A single publication compared tiotropium with placebo using SF-36;[51] tiotropium provided statistically significant improvements in physical health domains (physical function, role physical and general health, as well as summary score) on all assessment days ($p<0.05$), with no effect on mental health summary.

Contrasting effects of tiotropium compared with placebo have been reported using Borg dyspnoea scores: a 42-day study found a statistically significant benefit of tiotropium on exercise performance,[58] whereas a 12-week study found no effect on exercise limitation, although tiotropium-treated patients achieved longer exercise time.[65]

Effect of tiotropium versus active comparators on quality of life

Table 3 summarises QoL outcomes in trials comparing tiotropium with active comparators.

Tiotropium monotherapy versus ipratropium

Compared with treatment with the short-acting anticholinergic

Table 2. Summary of SGRQ and TDI outcomes in randomised double-blind trials of tiotropium compared with placebo.

Citation	Patients	SGRQ	Transition Dyspnoea Index
50	25-week study; tiotropium 18 µg od vs placebo; n=234 with FEV_1 ≤60% predicted and ≤70% of FVC. Steroids, theophylline, mucolytics, salbutamol (albuterol) allowed	SGRQ total scores reduced for tiotropium vs placebo (mean changes -7.3 vs -6.0 units on day 176; p=NS)	At end of PR (day 92), mean TDI focal score had increased more in the tiotropium vs placebo group (3.60 vs 2.25, p=0.001). Differences on days 29 and 176 were NS
52	25-week study; tiotropium 18 µg od vs placebo; n=108 with FEV_1 ≤60% predicted and ≤70% of FVC. Steroids, theophylline, salbutamol (albuterol) allowed	Tiotropium improved SGRQ total scores by 3.86 units vs placebo at the end of PR and 4.44 units 12 weeks after PR (both p>0.05)	8 weeks after PR, mean TDI focal scores increased (tiotropium 1.75, placebo 0.91). 12 weeks after PR, TDI focal score 0.08 for placebo; maintained at 1.75 for tiotropium (difference 1.67 units, p=0.03)
57; subgroup analysis of 52	25-week study; tiotropium 18 µg od vs placebo; n=46 with FEV_1 ≤60% predicted and ≤70% of FVC. Steroids, theophylline, salbutamol (albuterol) allowed	Tiotropium improved mean SGRQ total score by 3.83 units over placebo at end of 8-week rehabilitation (39.39 units tiotropium vs 43.22 units placebo) and by 5.64 units at study end (39.06 units vs 44.70 units, respectively). P values not reported	Tiotropium improved mean TDI focal score by 1.36 units over placebo at end of 8-week rehabilitation (2.80 units tiotropium vs 1.45 units placebo) and by 2.50 units at study end (3.08 vs 0.58 units). P values not reported
51	Two 1-year studies; tiotropium 18 µg od vs placebo; n=921 with FEV_1 ≤65% predicted and ≤70% of FVC. Steroids, theophylline, albuterol allowed	Mean total SGRQ score and each domain significantly improved (p<0.05) vs placebo for tiotropium at 12 months. Significantly more tiotropium patients (49%) had ≥4-unit total score improvement vs placebo (30%; p value not reported)	Mean TDI focal score significantly improved by day 50 for tiotropium vs placebo; maintained for 1 year. Differences 0.8–1.1 (p<0.001 all time points). More tiotropium patients achieved TDI focal score ≥1.0 at all assessments (42–47%) vs placebo (29–34%) (p<0.01)
59; secondary analysis of 51	Two 1-year studies; tiotropium 18 µg od vs placebo; n=921 with FEV_1 ≤65% predicted and ≤70% of FVC. Steroids, theophylline, salbutamol (albuterol) allowed. TIO-R or TIO-PR	Tiotropium significantly improved SGRQ total score vs placebo at 1 year for TIO-R (difference -3.96 units) and TIO-PR (difference -3.05 units); p<0.001. TIO-R vs TIO-PR, NS. More tiotropium patients achieved ≥4-unit change (TIO-R 51%, TIO-PR 48%, placebo 30%; p<0.05 for both vs placebo)	Significant improvements in TDI at 1 year; TIO-R 1.36, TIO-PR 0.86, vs placebo (p<0.001 for both; TIO-R vs TIO-PR p<0.05). Significantly more TIO-R and TIO-PR patients achieved TDI focal score ≥1.0 vs placebo (p<0.05)
60	4-year study; tiotropium 18 µg od vs placebo (UPLIFT®); n=5993 with FEV_1 ≤70% predicted and ≤70% of FVC. All medications allowed except other inhaled anticholinergics	Tiotropium significantly improved SGRQ total score vs placebo at all time points (difference -2.3 to -3.3 units, p<0.001; mean difference -2.7 units, p<0.001). More tiotropium patients improved total score ≥4 units from baseline at 1 year (49% vs 41%), 2 years (48% vs 39%), 3 years (46% vs 37%), 4 years (45% vs 36%) (p<0.001 for all). Differences in SGRQ rate of decline from 6 months to study end, NS	Not reported
56; secondary analysis of 60 (UPLIFT®)	4-year study; tiotropium 18 µg od vs placebo; n=5783 with bronchodilator responsiveness data and FEV_1 ≤70% predicted and ≤70% of FVC. All medications allowed except other inhaled anticholinergics	Patients with initial FEV_1 response ≥12% and 200 mL had SGRQ total score 1-year change -3.1 (vs -2.3 for non-responders). In patients with initial FEV_1 response ≥15%, SGRQ total score change -2.7 (vs -2.8). P values not reported	Not reported
53; secondary analysis of 60 (UPLIFT®)	4-year study; tiotropium 18 µg od vs placebo; n=356 aged ≤50 years with FEV_1 ≤70% predicted and ≤70% of FVC. All medications allowed except other inhaled anticholinergics	Difference (improvement) in SGRQ total score (tiotropium minus placebo) -3.5 at 1 year (p<0.05), -3.0 at 2 years (p<0.05), -4.2 at 3 years (p<0.05), 0.9 at 4 years (p>0.05)	Not reported
55; secondary analysis of 60 (UPLIFT®)	4-year study; tiotropium 18 µg od vs placebo; n=2739 patients with moderate COPD (GOLD stage II) with FEV_1 ≤70% predicted and ≤70% of FVC. All medications allowed except other inhaled anticholinergics	Tiotropium improved SGRQ total score and all domains by 2.7–4.0 units (total score), 2.3–3.9 units (impact), 2.7–4.1 units (symptom), 3.1–4.4 units (activity) vs placebo (p≤0.006 all time points)	Not reported
61; secondary analysis of 60 (UPLIFT®)	4-year study; tiotropium 18 µg od vs placebo; n=5993 with FEV_1 ≤70% predicted and ≤70% of FVC. All medications allowed except inhaled other anticholinergics	At 4 years, SGRQ total score improved most in continuing smokers (tiotropium minus placebo, -4.63 units, p<0.001), less in continuing ex-smokers (-2.74 units, p<0.001), least in intermittent smokers (-0.60 units, p=0.514). Reflected in all 3 domains	Not reported
63; secondary analysis of 60 (UPLIFT®)	4-year study; tiotropium 18 µg od vs placebo; patients with FEV_1 ≤70% predicted and ≤70% of FVC taking concomitant LABA (n=2982), ICS (n=2902), or LABA+ICS (n=2260). All medications allowed except other inhaled anticholinergics	4-year change in SGRQ total score (tiotropium minus placebo) -2.8 to -1.5 (LABA), -3.2 to -2.1 (ICS), -3.1 to -1.7 (LABA+ICS), all p<0.01	Not reported
64; secondary analysis of 60 (UPLIFT®)	4-year study; tiotropium 18 µg od vs placebo; n=810 receiving no maintenance therapy at baseline, with FEV_1 ≤70% predicted and ≤70% of FVC. All medications allowed except other inhaled anticholinergics	Decline in SGRQ total score slower for tiotropium vs placebo (difference 1.05 units/year, p=0.002), also for impact (1.08 units/year, p=0.004) and activity (1.44 units/year, p<0.001), but not symptoms (0.26 units/year, p=0.6). At 48 months, SGRQ total score improvement, tiotropium minus placebo, 4.6 units (p<0.001)	Not reported
54	48-week study; tiotropium 18 µg od vs placebo; n=913 with FEV_1 ≤65% predicted and ≤70% of FVC. Steroids, theophylline, mucolytics, LABAs, salbutamol (albuterol) allowed	Tiotropium significantly improved SGRQ symptom (44.4 vs 49.3), impact (28.5 vs 31.3) and total (40.9 vs 43.7) scores vs placebo, week 48 (p<0.01 for all). 53% (tiotropium) vs 44% (placebo) patients had ≥4 units improvement in SGRQ total score (p=0.052)	Not reported

continued overleaf

Table 2. Summary of SGRQ and TDI outcomes in randomised double-blind trials of tiotropium compared with placebo continued.

Citation	Patients	SGRQ	Transition Dyspnoea Index
58	42-day study; tiotropium 18 µg od vs placebo; n=261 with FEV_1 ≤65% predicted and functional residual capacity ≥120% predicted. Steroids, theophylline, mucolytics, salbutamol (albuterol) allowed	Not reported	Not reported
62	9-month study; tiotropium 18 µg od vs placebo; n=554 with FEV_1 20–70% predicted and ≤70% of slow vital capacity. Steroids, theophylline, salbutamol (albuterol) allowed	59.1% tiotropium vs 48.2% placebo patients achieved ≥4 unit SGRQ total score reduction, 9 months (p=0.029). Tiotropium significantly improved SGRQ total score vs placebo (all days p<0.05). At 9 months, mean difference in SGRQ total score -4.19 vs placebo, p=0.001). All 3 domains improved at study end (p<0.05 vs placebo). SGRQ improved most in most severe patients	Not reported
65	12-week study; tiotropium 18 µg od vs placebo; n=100 with FEV_1 ≤50% predicted and ≤70% of slow vital capacity. Steroids, theophylline, mucolytics, salbutamol (albuterol) allowed	Tiotropium improved SGRQ total score by 6.5 units at 12 weeks (p=0.026). 59% tiotropium and 35% placebo patients had improvements of ≥4 units in SGRQ total score (p<0.05)	TDI focal score (tiotropium minus placebo) 1.28 units at 12 weeks (p=0.15)
73	Two 6-month studies; tiotropium 18 µg od vs salmeterol 50 µg bid vs placebo; n=1207 with FEV_1 ≤65% predicted and ≤70% of FVC. Concomitant medication, including steroids and theophylline, allowed	SGRQ total score improved by 4.2 (tiotropium), 2.8 (salmeterol), and 1.5 (placebo) units over 6 months (tiotropium vs placebo p<0.01). Patients achieving ≥4 unit change 48.9% (tiotropium), 43.2% (salmeterol), and 39.3% (placebo); p<0.05 tiotropium vs placebo	TDI focal score improved for tiotropium (1.1 units, p<0.001) and salmeterol (0.7 units, p<0.05) vs placebo at 6 months (tiotropium vs salmeterol p=0.17). More patients achieved ≥1 unit change with tiotropium (43.1%) and salmeterol (41.2%) than placebo (29.8%, p<0.01)

bid: Twice daily; COPD: Chronic obstructive pulmonary disease; FEV_1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; ICS: Inhaled corticosteroids; LABA: Long-acting β-agonist; NS: Not significant; od: Once daily; PR: Pulmonary rehabilitation; SGRQ: St George's Respiratory Questionnaire; TDI: Transitional Dyspnea Index; TIO-R: Tiotropium-responsive; TIO-PR: Tiotropium-poorly responsive.

agent ipratropium, tiotropium monotherapy resulted in statistically (but not clinically) significant mean improvements in SGRQ total score (difference 3.3 units, p=0.004) and TDI focal score (difference 0.9 units, p=0.001) at one year, with significantly more tiotropium patients achieving clinically meaningful improvements in both measures.[70] This study also reported SF-36 outcomes, finding that tiotropium was more effective than ipratropium in all physical domains (although differences between groups were only significant in physical health summary on days 273 and 364), with no effect on mental health domains.[70]

Tiotropium monotherapy versus salmeterol

In two identical 6-month studies there were numerical improvements in mean SGRQ total score with tiotropium monotherapy versus monotherapy with the LABA salmeterol (difference, 1.4 units; statistical significance not reported); the difference (0.4 unit improvement with tiotropium vs salmeterol) for the mean TDI focal score was not statistically significant.[73]

Tiotropium versus dual therapy (salmeterol plus fluticasone)

A 2-year trial reported that the mean SGRQ total score was statistically (but not clinically) significantly improved with combination salmeterol and the ICS fluticasone propionate (SFC) compared with tiotropium monotherapy (difference 2.1 units, p=0.038).[71] This improvement appeared to be driven predominantly by differences in the impacts domain; TDI was not reported.[71] A significantly higher proportion of SFC (32%) than tiotropium (27%, p=0.021) patients achieved a clinically meaningful change in SGRQ.[71] In a 14-day study assessing TDI, numerically greater improvements were reported with SFC versus tiotropium; however, there was no formal statistical comparison between the groups.[68]

Tiotropium versus tiotropium plus another agent (dual therapy)

A 1-year comparison of tiotropium monotherapy with tiotropium plus salmeterol found statistically (but not clinically) significantly greater improvements in SGRQ total score for the dual therapy (difference 1.8 units, p=0.02), but no difference in TDI.[66]

The addition of formoterol fumarate (a LABA) to tiotropium resulted in little benefit over tiotropium monotherapy in terms of SGRQ in two 6-week studies.[67,69] The only (clinically and statistically) significant change was observed in the symptom score for dual therapy versus monotherapy in one study.[69] In terms of TDI scores, there was a significantly greater improvement with dual therapy in one trial[69] but not the other;[67] more patients had improvements in dyspnoea in the dual therapy versus monotherapy group in both studies.[67,69]

Tiotropium versus tiotropium plus two other agents (triple therapy)

Comparisons of tiotropium monotherapy with tiotropium plus two other therapies have shown the benefit of triple therapy. A 1-year comparison of tiotropium monotherapy with tiotropium plus SFC found statistically and clinically significant greater improvements in SGRQ total score for triple therapy (difference 4.1 units, p=0.01), but no statistically significant difference in TDI (difference 0.06 units, p=0.38).[66] However, a

Table 3. Summary of SGRQ and TDI outcomes in randomised double-blind trials of tiotropium compared with active comparators.

Citation	Interventions	SGRQ	Transition Dyspnoea Index
66	1-year study; tiotropium 18 µg od plus placebo vs tiotropium 18 µg od plus salmeterol 50 µg bid vs tiotropium 18 µg od plus SFC 500/50 µg bid; n=449 with FEV_1 <65% predicted and ≤70% of FVC. Salbutamol (albuterol), antileukotrienes, methylxanthines allowed	1-year change in SGRQ total score -6.3 (tiotropium plus salmeterol; p=0.02 vs tiotropium plus placebo), -8.6 (tiotropium plus SFC; p=0.01 vs tiotropium plus placebo), and -4.5 (tiotropium plus placebo)	Mean TDI scores at 1 year 1.40 (tiotropium plus salmeterol; p=0.35 vs tiotropium plus placebo), 1.84 (tiotropium plus SFC; p=0.38 vs tiotropium plus placebo) and 1.78 (tiotropium plus placebo)
73	Two 6-month studies; tiotropium 18 µg od vs salmeterol 50 µg bid vs placebo; n=1207 with FEV_1 ≤65% predicted and ≤70% of FVC. Concomitant medication, including steroids and theophylline, allowed	SGRQ total score improved by 4.2 (tiotropium), 2.8 (salmeterol), and 1.5 (placebo) units over 6 months (tiotropium vs placebo, p<0.01). Patients achieving ≥4 unit change 48.9% (tiotropium), 43.2% (salmeterol), and 39.3% (placebo); p<0.05 tiotropium vs placebo	TDI focal score improved for tiotropium (1.1 units, p<0.001) and salmeterol (0.7 units, p<0.05) vs placebo at 6 months (tiotropium vs salmeterol, p=0.17). More patients achieved ≥1 unit change with tiotropium (43.1%) and salmeterol (41.2%) than placebo (29.8%, p<0.01)
67	6-week study; tiotropium 18 µg od plus formoterol 20 µg bid vs tiotropium 18 µg od plus placebo; n=155 with FEV_1 ≥25% and <65% predicted, and ≤70% of FVC. Steroids, salbutamol (albuterol) allowed	At 6 weeks, no significant difference between groups in total or component SGRQ scores. More tiotropium plus formoterol (61%) than tiotropium plus placebo (25%) patients improved ≥4 units	At 6 weeks, a higher but not statistically significant difference between groups in TDI (1.59 vs 0.87). More tiotropium plus formoterol patients (58%) than tiotropium plus placebo patients (47%) showed improvement >1 unit
68	3-way crossover study (14 days each regimen); SFC 50/500 µg bid plus tiotropium 18 µg od vs SFC vs tiotropium; n=41 with FEV_1 >30% and ≤75% predicted, and ≤70% of FVC. Salbutamol (albuterol) allowed	Not reported	Significant difference in total TDI score for SFC plus tiotropium (2.3) vs tiotropium alone (0.2) at day 14 (difference 2.2 units; p<0.001) but not for SFC plus tiotropium vs SFC alone (difference 0.7 units, p=0.24). 72% of patients improved ≥1 unit on SFC plus tiotropium, 27% tiotropium alone, 54% SFC alone. P value not reported
69	6-week study; tiotropium 18 µg od vs combined tiotropium 18 µg od plus formoterol 20 µg bid; n=130 with FEV_1 ≥25% and <65% predicted, and ≤70% of FVC. Steroids, salbutamol (albuterol) allowed	No change in scores over 6 weeks. Improved change from baseline in symptom score for combined vs monotherapy (-5.8 units vs +0.5 units respectively, p=0.04)	Mean TDI scores at 6 weeks 2.30 (combined) and 0.16 (monotherapy) (difference 1.80, p=0.0002). 57.7% of combined patients improved dyspnoea from baseline. 68.9% monotherapy patients had no change/worsening dyspnoea. No combined patients had major/moderate worsening dyspnoea
70	Two 1-year studies; tiotropium 18 µg od vs ipratropium 40 µg qid; n=535 with FEV_1 ≤65% predicted, and ≤70% of FVC. Theophylline, steroids, salbutamol (albuterol) allowed	Over 1 year, improved SGRQ total score gradually returned towards baseline with ipratropium, but maintained for tiotropium (difference 3.30 units at 1 year, p=0.004). Compared with ipratropium, tiotropium improved symptom (-3.15 units; p=0.07), activity (-1.14 units; p=0.40) and impact (-4.28; p=0.006) domains. More tiotropium patients had ≥4 units improvement in SGRQ total score (52% vs 35% for ipratropium at 1 year, p=0.001)	TDI focal score and 3 components improved with tiotropium vs ipratropium (all days; p<0.05). Difference in focal score 0.9 units at 1 year (p=0.001). More tiotropium (31%) than ipratropium (18%) patients had ≥1 unit change in focal score at 1 year (p=0.004)
71	2-year study (INSPIRE); tiotropium 18 µg od vs SFC 50/500 µg bid; n=1323 with FEV_1 <50% predicted. Steroids, antibiotics, short-acting β-agonists allowed	SGRQ total score significantly lower at 2 years for SFC versus tiotropium (difference -2.1 units; p=0.038). More SFC patients (32%) had a clinically significant improvement in SGRQ at 2 years than tiotropium (27%; p=0.021)	Not reported
72	12-week study; tiotropium 18 µg od vs tiotropium 18 µg od plus budesonide/formoterol 320/9 µg bid; n=660 with FEV_1 ≤50% predicted. Terbutaline allowed	Over 12 weeks, SGRQ-C total score improved by 3.8 units with triple therapy vs 1.5 units for monotherapy (mean difference, -2.3; p=0.023). Improvements in total score >4 units in 49.5% (triple therapy) and 40.0% (monotherapy) of patients (p=0.016)	Not reported

bid: Twice daily; FEV_1: Forced expiratory volume in 1 second; NS; Not significant; od: Once daily; qid: 4 times daily; SFC: Salmeterol plus fluticasone propionate; SGRQ: St George's Respiratory Questionnaire; TDI, Transitional Dyspnoea Index.

14-day comparison of tiotropium alone with tiotropium plus SFC found both statistically and clinically significant improvements in TDI total score with triple therapy compared with tiotropium monotherapy (difference 2.2 units, p<0.001), but no statistically significant difference versus SFC monotherapy.[68] More triple-therapy patients (72%) than monotherapy patients (27%, p value not reported) achieved a clinically important change in TDI.[68] A 12-week comparison of tiotropium plus placebo with tiotropium plus budesonide/formoterol found statistically (but not clinically) significant improvements in SGRQ score with triple therapy compared with tiotropium monotherapy.[72] In addition, significantly greater numbers of triple-therapy patients achieved clinically meaningful changes in SGRQ scores.[72]

Discussion

This systematic review shows that tiotropium has a benefit on QoL. Compared with placebo, tiotropium statistically significantly improved SGRQ[51,54,60,62,73] and TDI[51,52,73] in most of the studies that were analysed. In other studies, numerical, but not statistically significant improvements in SGRQ total score[50,52] and TDI[50,65] were observed. Clinically significant improvements of ≥4 units in SGRQ total score were achieved in some shorter-term (<9 months duration) studies,[52,62,65] but not others.[50,51,60,54,73]

Table 4. Comparison of quality-of-life outcomes in placebo-controlled trials* of tiotropium monotherapy.

Reference	Trial duration	SGRQ				TDI			
		Mean total score (tiotropium minus placebo), units	P value	% patients achieving MCID (tiotropium vs placebo)	P value	Mean focal score (tiotropium minus placebo), units	P value	% patients achieving MCID (tiotropium vs placebo)	P value
65	12 weeks	-6.5	=0.026	59% vs 35%	<0.05	1.28	=0.15	NR	
50	25 weeks	-1.3	NS	NR		approx 0.5	NS	NR	
52	25 weeks	-4.44	NS	NR		1.67	0.03	NR	
73	6 months	-2.7	<0.01	48.9% vs 39.3%	<0.05	1.1	<0.001	43.1% vs 29.8%	<0.01
62	9 months	-4.19	=0.001	59.1% vs 48.2%	=0.029	NR		NR	
54	48 weeks	-2.8	<0.01	53% vs 44%	=0.052	NR		NR	
51	1 year	approx -3.8	<0.05	49% vs 30%	NR	approx 1.1	<0.001	approx 47% vs 34%	<0.01
60	4 years	-2.7	<0.001	45% vs 36%	<0.001	NR		NR	

MCID: Minimal clinically important difference; NR: Not reported; NS: Not significant; SGRQ: St George's Respiratory Questionnaire; TDI: Transition Dyspnoea Index.
* Primary data only are included in this table – duplicate data, secondary analyses, and subgroup analyses are not included (see Tables 2 and 3).

Tiotropium provided clinically meaningful improvements of ≥1 unit compared with placebo in almost all studies in which TDI was assessed.[51,52,65,73] Tiotropium monotherapy had a significantly greater benefit than ipratropium monotherapy.[70] Findings from one study comparing tiotropium with salmeterol monotherapy showed numerical but not statistically significant improvements with the anticholinergic agent.[73] Treatment with SFC improved health status versus tiotropium monotherapy – although, notably, a statistically significant difference was reported in only one of the two studies comparing the two treatment regimens.[71] Further benefits were seen when other drugs were added to tiotropium therapy – for example, with the addition of salmeterol[66] but not with formoterol.[67,69] Comparisons of tiotropium monotherapy with triple therapy (tiotropium plus two other therapies) showed the potential clinical advantages of this latter approach to treatment.[66,68,72]

It should be noted that, while the UPLIFT® trial compared tiotropium monotherapy to placebo (control), its study design means that the comparison was made in the context of a background of "any other respiratory medication". This is because patients in both the tiotropium and control arms were allowed to receive additional therapies: >70% of patients received concomitant LABAs and/or ICS during the study.[60] Significant improvements in SGRQ scores were observed with tiotropium versus control, suggesting an additional benefit of tiotropium (tiotropium dual or triple therapy) compared with LABA or ICS alone.[60] Interestingly, clinically significant improvements were observed with tiotropium in subgroups of patients suggestive of earlier disease in UPLIFT®, namely GOLD Stage II patients and those not previously receiving maintenance therapy,[55,64] in addition to continuing smokers.[61] These subgroup analyses of UPLIFT®, while prespecified (protocol-defined), should be considered hypothesis-generating only. The benefit of tiotropium in these patient subgroups requires confirmation in further clinical studies.

The current findings support the conclusions of an earlier systematic review, where meta-analysis confirmed the significant benefits for tiotropium in terms of SGRQ, although the TDI data were inadequate for meta-analysis.[74] However, it should be noted that this previous meta-analysis used many of the data included in the current up-to-date systematic review.

This current study has some limitations. The search was restricted to English-language publications and mainstream journals and congresses, so could not capture data published elsewhere. The body of evidence is based mostly on secondary endpoints (Table 1), and QoL was the primary endpoint in only one study.[62] The vast majority of QoL data were derived from just two outcome measures (SGRQ and TDI), and TDI assesses only one aspect of QoL (dyspnoea). In addition, many studies did not provide the data for individual SGRQ domains. This makes it difficult to assess which aspects of QoL are driving the improvements in total scores, although the available data suggest that changes in SGRQ total score are driven by all three,[51,55,62] or two,[54] domains.

The reliance on SGRQ and TDI in RCTs is understandable because, although many other disease-specific and generic PROM instruments are available, not all have been rigorously validated. Following a review of the available evaluation and validity data for various PROM instruments in COPD, the SGRQ and CRQ were recommended among the disease-specific PROM instruments, and the SF-36 for generic PROM;[75] the TDI was not assessed, but has been validated elsewhere.[11,76] Of the available PROM instruments, the SGRQ and TDI provide some of the most robust and validated assessments of QoL. This lends credence to the benefit of tiotropium identified in the current systematic review. Other reviews of PROM instruments have been conducted, but with different aims.[77,78]

While the PROM instrument selected for use in a clinical trial must be robust and validated, it should also be applicable for use in day-to-day clinical practice. Although the SGRQ is used most frequently in clinical trials, it is lengthy and its interpretation in clinical practice can be difficult. Practicalities are important, and

older patients, or those with severe disease, may have difficulty completing questionnaires.[79] Consequently, there is a need for a validated, short, simple PROM instrument for use in clinical practice to quantify the impact of COPD on QoL. Furthermore, determining what level of change in QoL is clinically meaningful is also difficult. In clinical trials using the SGRQ, the minimal clinically important difference (MCID) is widely accepted to be a change of 4 units;[80] for the TDI, it is a change of 1 unit.[81] However, as the authors of the SGRQ acknowledge, this is an average score obtained in different groups of patients and is an indicative value rather than an absolute threshold. In the study from which the value of 4 units was derived for COPD patients, a mean improvement of 2 units was reported among those who described treatment as "satisfactory", while a mean improvement of 4.3 units was seen in patients in whom a very clear efficacy advantage of treatment was perceived – i.e. those who reported the treatment as "effective".[82] It would be interesting to explore the threshold at which the actual minimal level of improvement is perceived by COPD patients for this PROM.

In COPD, QoL is of prime concern to the patient, as this is how they perceive their illness. Impaired ability to perform basic activities of daily living (e.g. washing, dressing, cooking), impaired exercise tolerance (e.g. breathlessness preventing social activities or climbing stairs), and exacerbations (repeated debilitating episodes, often requiring hospitalisation) all greatly affect their life. Exacerbations have a sustained effect on health status (SGRQ), and QoL is particularly affected by repeated exacerbations.[83] That said, QoL does not necessarily correlate closely with all objective measures of disease progression favoured by physicians and clinical trials. While measures of lung function correlate moderately with measures of physical function, the correlation with measures of psychosocial function is small, and the correlation with measures of emotional status is non-significant.[84] Targeting an improvement in forced expiratory volume in 1 second (FEV_1) may have a beneficial effect on physical functioning but is less likely to affect psychosocial function and emotional status.[84] Therefore, thoroughly assessing the impact of COPD on the patient requires a battery of PROM instruments, including disease-specific and generic tools.[84]

Patients with COPD who are managed in primary care may require special consideration. A cohort study found that those with a higher SGRQ total score (i.e. worse QoL) had a longer evolution of COPD, more severe dyspnoea, and a worse FEV_1.[39] Factors independently associated with the total SGRQ score were cough and dyspnoea, duration of COPD, and treatment with inhaled steroids.[39] Strategies aimed at modifying chronic cough and dyspnoea may significantly improve patients' well-being.

Conclusions

COPD is characterised by limitation of airflow that is not completely reversible, and loss of lung function is progressive over time. Optimising HRQoL is of utmost importance to patients with COPD, and should be an important outcome and disease measurement for researchers and physicians. This systematic review has shown that treatments such as tiotropium can provide significant improvements in QoL. Tiotropium improves QoL in patients with COPD who require long-acting bronchodilator treatment, and other additional therapies provide further benefits, depending on the population.

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Conflict of interest declarations

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