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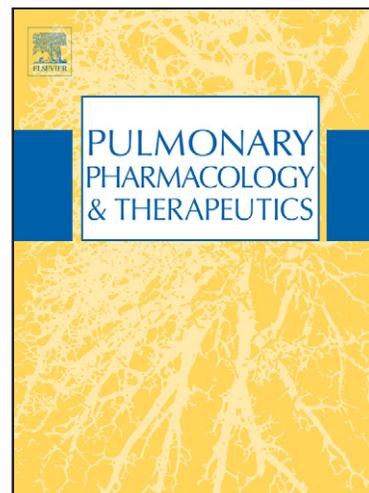
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7 **Tiotropium improves FEV₁ in patients with COPD**
8 **irrespective of smoking status**
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28

28 **Abstract**

29

30 This study evaluated whether the effect of tiotropium on the change in trough forced
31 expiratory volume in 1 second (FEV₁), vs. placebo, is affected by smoking status. In a 3-
32 month, double-blind study in 31 centres in Portugal, 311 (289 completed) patients were
33 randomised to tiotropium 18 µg once daily or placebo. Baseline mean (standard deviation
34 (SD)) FEV₁ was 1.11 (0.39) l in the tiotropium group and 1.13 (0.39) l in the placebo group.
35 Patients had an average smoking history of 55 (25.7) pack-years; 80 (26%) were smokers
36 and 224 (74%) were ex-smokers. The primary end point was change in morning pre-dose
37 (i.e. trough) FEV₁ after 12 weeks. Trough FEV₁ at 12 weeks was significantly improved
38 with tiotropium vs. placebo: the difference in means was 102 ml, P=0.0011, 95%
39 confidence interval (CI) (41, 164). The difference in means in smokers was 138 ml,
40 P=0.0105, CI (32, 244); in ex-smokers it was 66 ml, P=0.0375, CI (3, 129). The difference
41 between smokers and ex-smokers was not statistically significant (P=0.6982) and may be
42 due to greater variability and differences in disease severity. The significant improvement
43 in lung function in patients treated with tiotropium vs. placebo in both smokers and ex-
44 smokers suggests that tiotropium is an effective and well-tolerated therapy in chronic
45 obstructive pulmonary disease (COPD), regardless of smoking status.

46

47 *Keywords:* Tiotropium; Lung function; FEV₁; Smoking status; COPD

48

48 1. Introduction

49

50 Cigarette smoking is a major risk factor for the development of chronic obstructive
51 pulmonary disease (COPD) in susceptible individuals worldwide and may account for up to
52 90% of the risk in developed countries [1–3]. Evidence suggests that the number of years
53 spent as a smoker and amount of cigarettes smoked impacts on the prevalence of
54 respiratory symptoms, exacerbations, rate of decline in lung function (i.e. forced expiratory
55 volume in 1 second [FEV₁]) and COPD-related mortality [4–7]. Cigarette smoking is
56 thought to exert its effects via increased inflammation, airway wall fibrosis, destruction of
57 alveolar attachments, and inhibition of repair mechanisms [2,8].

58 Currently, smoking cessation is the only intervention shown to slow the long-term
59 progression of airflow obstruction as measured by the decline in FEV₁ [1]. However,
60 smoking cessation is far from easy and smoking cessation programmes generally have
61 poor success rates [9–11]. Evidence also suggests that chronic inflammation persists after
62 smoking has stopped [12], which will continue to contribute to lung function decline.
63 Hence, it is important to identify treatments that benefit patients with COPD, despite the
64 fact that they might continue to smoke.

65 Tiotropium is a once-daily maintenance treatment for COPD that provides 24-hour
66 efficacy due to prolonged M₃-receptor antagonism. It has consistently been shown to
67 improve lung function, exercise tolerance and health status, and reduce dyspnea in
68 patients with COPD [13–15]. Post hoc analysis of two combined 1-year placebo trials has
69 also provided preliminary evidence to suggest that long-term maintenance treatment with
70 tiotropium once daily may slow the decline in trough (i.e. morning pre-dose) FEV₁
71 compared with placebo [16]; a possibility that is currently specifically being investigated in
72 a 4-year prospective trial [17].

73 The rationale for performing this trial was based on a meta-analysis from seven
74 clinical trials with the shorter-acting anticholinergic, ipratropium, in patients with moderate
75 to severe COPD, which suggested that the improvement in baseline lung function in
76 ipratropium-treated patients was greater in ex-smokers than in smokers [18]. The aim of
77 this study, entitled 'Spiriva[®] Assessment of FEV₁' (SAFE), was to evaluate whether the
78 effect of tiotropium on the change in trough FEV₁ is affected by smoking status.

79

79 2. Methods

80

81 2.1. Study design

82

83 This was a randomised, double-blind, parallel-group, placebo-controlled, 3 month
84 study conducted in 31 centres in Portugal. The study (#205.282) was designed to
85 determine whether the effect of tiotropium on trough FEV₁ in patients with COPD was
86 affected by smoking status. The study was approved by regulatory and ethics committees
87 at all centres.

88

89 2.2. Subjects

90

91 Males or females aged ≥ 40 years with a diagnosis of COPD (FEV₁ $\leq 70\%$ of
92 predicted and FEV₁/forced vital capacity (FVC) $\leq 70\%$ [19]) and a smoking history of ≥ 10
93 pack-years were eligible for inclusion.

94 Patients were asked about their smoking status on the first visit. Smoking status
95 consisted of two categories: smokers and ex-smokers (0 cigarettes/day).

96 Patients were not included if they had a history of asthma, allergic rhinitis, atopy,
97 myocardial infarction, unstable arrhythmia, or if they had any clinically significant disease
98 that might put the patient at risk because of study participation. Patients with ≥ 3
99 exacerbations of COPD in the preceding year or an exacerbation or lower respiratory tract
100 infection within the 6 weeks prior to randomisation were also excluded.

101 Concomitant use of prn salbutamol MDI (100 μg /puff; withheld for at least 6 hours
102 prior to each clinic visit), long-acting β_2 -agonists and continued use of theophylline
103 preparations (excluding 24-hour preparations) (both withheld for at least 24 hours prior to
104 each clinic visit) were allowed during the study period. Concomitant use of mucolytics,
105 orally inhaled corticosteroids, minimal doses of oral corticosteroids (equivalent to
106 prednisone ≤ 10 mg/day or ≤ 20 mg/alternate days) were allowed if the dosage was
107 stabilized for at least 6 weeks before the study. Temporary increases in the dose of
108 theophylline preparation of ≤ 7 days or addition/increased dose of oral steroids for ≤ 2
109 weeks were allowed for the treatment of an exacerbation during the study period. If
110 appropriate, scheduled visits were postponed for at least 1 week, but not more than 2
111 weeks. Use of antibiotics was not restricted. Short-acting anticholinergics, oral β_2 -agonists,
112 antileukotrienes, and other investigational drugs were not allowed during the study.

113 2.3. Assessments

114

115 After a 2-week run-in period, patients were randomised to receive tiotropium 18 µg
116 once daily, delivered via the HandiHaler® device (Boehringer Ingelheim, Ingelheim am
117 Rhein, Germany), or placebo for 12 weeks. FEV₁ and FVC were measured on test days at
118 10 minutes (±5 minutes) prior to administration of study drug (trough). Measurements were
119 performed in triplicate using a Datospir 120C spirometer (Sibelmed, Barcelona, Spain) in
120 accordance with American Thoracic Society criteria [20].

121 The primary end point was the change in trough FEV₁ after 12 weeks of treatment.
122 Trough FEV₁ was measured 24 hours after the previous dose of study drug on Day 1
123 (randomisation) as well as after 6 and 12 weeks of treatment. Secondary end-points
124 included trough FEV₁ after 6 weeks of treatment, trough FVC after 6 and 12 weeks of
125 treatment, assessment of COPD symptoms, Physician's Global Evaluation, Quality of Life
126 Questionnaire (EQ-5D) and use of daytime and night-time rescue medication (salbutamol
127 MDI 100 µg/puff). Rescue medication use, cigarette consumption and drug compliance
128 were recorded in patient diary cards. Adverse events were collected throughout the study.

129

130 2.4. Statistical analysis

131

132 For the primary end point, the comparison between tiotropium and placebo was
133 assessed via an analysis of covariance (ANCOVA) model, with treatment and centre as
134 fixed effects, and mean trough FEV₁ baseline as covariate. The primary end point was
135 also stratified according to smoking status (smokers and ex-smokers), which was added to
136 the ANCOVA model as a fixed effect. The least square mean (LSM) for FEV₁ response
137 was computed and compared for each treatment group, stratified by smoking status. The
138 secondary spirometry measures were also analyzed using a similar ANCOVA model. The
139 COPD symptoms and global evaluation by investigator were analysed only descriptively.
140 The EQ-5D questionnaire was evaluated following EuroQol Group Enterprise conventions
141 [22]. Descriptive statistics were used for safety variables.

142 Efficacy analyses were performed using the Full Analysis Set (FAS), which
143 included all patients who received at least one dose of treatment and had at least a
144 baseline value and who did not change smoking status during the trial. The Safety
145 Analysis Set (SAS) included all patients who received at least one dose of treatment and
146 had one safety evaluation after treatment.

147 To detect a difference of 130 ml with 90% power based on a SD of 215 ml, 59
148 patients were required in each treatment group. In order to obtain 59 ex-smokers in the
149 placebo group, based on assumed ratio of smokers to ex-smokers of 3:2, a total of 148
150 patients were required in each treatment group.

151 **3. Results**

152

153 *3.1. Subjects*

154

155 A total of 335 patients were screened and 311 were randomised to treatment.
156 Seven patients changed their smoking status during the 12 weeks after randomisation,
157 and were excluded from the study. A total of 304 patients were included in the Full
158 Analysis Set (tiotropium: 144; placebo: 160) (Table 1). The baseline characteristics for the
159 remaining 304 patients were comparable across treatment groups (Table 1).

160 Patients had a mean smoking history of 55 pack-years, and 80 (26%) were
161 smokers and 224 (74%) were ex-smokers. A greater proportion of ex-smokers (27%) had
162 very severe disease (defined as $FEV_1/FVC < 70\%$ and $FEV_1 < 30\%$ predicted) compared
163 with smokers (19%). In the tiotropium treatment group, the study was unable to provide
164 smoker and ex-smoker groups with comparable baseline characteristics for smoking
165 history and FEV_1 . Compared with ex-smokers in the tiotropium group, smokers in the
166 tiotropium group had a higher pack-year smoking history (5.6 pack-years) and a higher
167 FEV_1 (0.20 L). The percentage completing the study according to protocol was high at
168 92.9% (289/311) (Table 2).

169

170 *3.2. Efficacy assessments*

171

172 In the overall group population, tiotropium significantly improved the mean trough
173 FEV_1 at 12 weeks compared with placebo, with a mean difference of 102 ml ($P=0.001$)
174 (Table 3).

175 Compared with placebo, tiotropium significantly improved mean trough FEV_1 after
176 12 weeks in both smokers and ex-smokers though the variability was greater with smokers
177 (Figure 1). At study end, the mean difference between the tiotropium and placebo groups
178 was 138 ml ($P=0.011$) in the smokers group, and 66 ml ($P = 0.038$) in the ex-smokers
179 group. The difference between smokers and ex-smokers was not statistically significant
180 ($P=0.698$).

181 A similar trend was also observed for trough FEV₁ at 6 weeks. The mean difference
182 between the tiotropium and placebo groups was 94 ml (95% CI: 154, 34; P=0.022). The
183 difference between treatment groups was 121 ml (95% CI: 226, 15; P=0.025) for smokers
184 and 67 ml (95% CI: 124, 10; P=0.021) for ex-smokers. There was no evidence of
185 tachyphylaxis (Figure 1).

186 The mean change from baseline in trough FEV₁ was generally higher in smokers
187 than in ex-smokers.

188 Tiotropium significantly improved mean trough FVC after 12 weeks compared with
189 placebo (P=0.019) (Table 3). Improvements compared with placebo occurred in both
190 smokers and ex-smokers, though they were significant only in ex-smokers. However, the
191 difference between responses to tiotropium in smokers and ex-smokers was not
192 statistically significant (P=0.535).

193 Compared with placebo, patients in the tiotropium group used fewer doses of
194 daytime and night-time rescue medication during the study. This difference tended to
195 increase over the 12-week treatment period. The difference in daytime usage between
196 placebo and tiotropium was significant at Weeks 2, 6, 8, 11 and 12 (P<0.05). The
197 magnitude of the reduction in daytime rescue medication use with tiotropium compared
198 with placebo tended to be greater in smokers than ex-smokers in the latter 6 weeks of
199 treatment (Figure 2). Similar trends were seen with night-time rescue medication.

200 COPD symptoms, global evaluation by the investigator and the EQ-5D showed no
201 differences between treatment groups.

202

203

204 3.3 Safety assessment

205

206 The proportion of patients experiencing at least one adverse event during the study
207 was 11.6% in the tiotropium group and 15.9% in the placebo group. Six patients (4.1%) in
208 the tiotropium group and three patients (1.8%) in the placebo group experienced a serious
209 adverse event, including two deaths (both in the tiotropium group), but none of these nine
210 events was considered to be related to study medication.

211 Respiratory system disorders were distributed in three different groups: lower
212 (including COPD exacerbations), upper and other. The results showed that the most
213 commonly reported adverse events in both the tiotropium and placebo groups were: Lower
214 Respiratory disorders (18.3% and 20.1%, respectively); and Upper Respiratory disorders

215 (5.4% and 4.9%, respectively) (Table 4).

216 **4. Discussion**

217

218 The aim of this study was to determine whether the effect of inhaled tiotropium on
219 lung function in patients with COPD was affected by smoking status. The primary outcome
220 of this study showed that there was a significant improvement in trough FEV₁ after 12
221 weeks' treatment with tiotropium compared with placebo, irrespective of smoking status.
222 These data were supported, at least in part, by the secondary outcomes.

223 The use of short-acting bronchodilators for symptomatic relief provides an
224 indication of the degree of dyspnea experienced by the patient. Tiotropium reduced
225 daytime and night-time rescue medication compared with placebo during the study, and
226 the difference between active treatment and placebo tended to increase over the 12-week
227 treatment period. Subgroup analysis suggests that the mean response to tiotropium for
228 reduction of daytime use of rescue medication was significantly greater in smokers
229 compared with ex-smokers. However, though a trend was evident at other time points, this
230 result may be related to greater variability within these subgroups and differences in
231 disease severity.

232 There have been few studies specifically analysing the relationship between
233 bronchodilators and smoking status. A meta-analysis of seven trials in moderate to severe
234 COPD has suggested that the bronchodilator response to the anticholinergic ipratropium
235 may be greater in ex-smokers compared with smokers [18]. Examination of the subgroup
236 of ex-smokers in these trials showed them to have a baseline FEV₁ of about 20% less than
237 smokers. Hence, the authors of the meta-analysis suggested that the greater response
238 with ipratropium in ex-smokers might be related to more severe impairment of lung
239 function. This result could have relevance in the interpretation of the Lung Health Study,
240 which suggested no sustained additional effect of ipratropium on the reduced rate of
241 decline in lung function as a result of a smoking cessation programme [21]. The Lung
242 Health Study recruited only current smokers, which, in addition to the reported use of an
243 average of two doses of ipratropium per day rather than the prescribed three to four doses
244 per day, could have limited the effect of ipratropium compared with that which may occur
245 in long-term ex-smokers.

246 Ideally, interventions in COPD need to be effective in both smokers and ex-
247 smokers, particularly as many patients find it difficult to stop smoking. However, smoking
248 cessation must be viewed as the most important therapeutic intervention for those who

249 continue to smoke and should be encouraged with the latest advances in treating nicotine
250 addiction whenever feasible. Bronchodilators are considered first-line maintenance therapy
251 in the management of symptomatic COPD [1]. Hence, the results of the current study
252 showing beneficial effects of tiotropium treatment on lung function in both smokers and ex-
253 smokers are encouraging. A trend for greater responses with tiotropium in smokers, which
254 is in contrast to the findings with ipratropium, may be suggested from some data in this
255 trial. Data from smokers showed greater variability than data from ex-smokers and a
256 greater proportion of ex-smokers had more severe disease than smokers, both of which
257 may account for the lack of statistical significance between groups. More severe disease in
258 ex-smokers was also shown in patients recruited in 1-year study trials with tiotropium [16].
259 In this case, the authors speculated that patients with more rapidly progressing disease
260 are more likely to have the incentive to stop smoking successfully compared with those
261 with more gradual disease progression.

262 There are several limitations to the current study. First, according to the protocol,
263 the proportions of smokers and ex-smokers were expected to be 60% and 40%,
264 respectively. However, the proportions were modified to 32% smokers and 68% ex-
265 smokers in order to achieve at least 85% statistical power in the analyses of smokers. Due
266 to enrolment difficulties the ratio of smokers to ex-smokers became more disproportionate.
267 As seven patients changed their smoking status during the study and were excluded from
268 the analyses, a total of 80 smokers were included in the trial (26.3% instead of the
269 expected 32%; 40 smokers per treatment arm), with this ratio the statistical power in the
270 analyses of smokers was 75%. Consequently, the proportion of smokers available for
271 analysis was lower than planned in the protocol, which may have increased the variability
272 in the data in the smokers subgroup. Second, as smoking abstinence was not verified by
273 saliva cotinine or expired carbon monoxide some patients may have been misclassified.
274 Third, the duration of 12 weeks may not be representative of the long-term effects of
275 maintenance treatment with tiotropium in patients with COPD stratified by smoking status.
276 Hence, further data from large, long-term trials with tiotropium, such as the ongoing, 4-year
277 Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT) trial [17]
278 are required to confirm these results.

279 In summary, tiotropium significantly improved lung function in both smokers and
280 ex-smokers compared with placebo. This, combined with a favourable safety profile from
281 this trial, suggests that tiotropium is an effective and well-tolerated therapy in COPD,
282 regardless of smoking status.

283

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301

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- 362

362 Table 1
 363 Demographic and baseline characteristics (full analysis set)

	Tiotropium (n=144)		Placebo (n=160)	
	Non-smokers	Smokers	Non-smokers	Smokers
Patients (n)	104	40	120	40
Males (%)	97	93	95	93
Age (years)*	65.7±8.6	61.6±9.8	65.7±9.0	64.0±7.2
Duration of COPD (years)*	14.0±10.9	9.4±6.8	13.7±10.5	12.3±8.5
Smoking history (pack-years)*	54.3±27.1	59.9±23.4	54.3±26.7	55.3±17.3
Duration of smoking cessation (years)*	9.1±9.8	0.0±0.0	10.2±10.4	0.0±0.0
Median (range) duration of smoking cessation (years)	5.6 (0.0–51.0)	0.0±0.0	6.1 (0.0–55.0)	0.0±0.0
FEV ₁ (L)*	1.06±0.37	1.26±0.42	1.13±0.40	1.15±0.40
FEV ₁ (% predicted)*	38.4±12.8	44.4±13.9	42.3±15.3	40.4±14.5
FVC (L)*	2.42±0.76	2.68±0.73	2.52±0.69	2.54±0.71
FEV ₁ /FVC (%)*	44.4±11.0	47.9±13.7	45.2±11.5	46.7±13.4

364
 365 *Mean (SD); FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity
 366

366 Table 2

367 Disposition of patients

368

369

	Tiotropium	Placebo	Total
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370

371

Patients randomised (%)	147(100.0)	164(100.0)	311(100.0)
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372 Completed study according

373 to protocol

	136(92.5)	153(93.3)	289(92.9)
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374 Reasons for premature

375 discontinuation:

376 Unexpected worsening of

377 COPD

	1(0.7)	2(1.2)	3(1.0)
--	--------	--------	--------

378 Unexpected worsening of

379 other pre-existing condition

	1(0.7)	0(0.0)	1(0.3)
--	--------	--------	--------

380 Lost to follow-up

	5(3.4)	4(2.4)	9(2.9)
--	--------	--------	--------

381 Consent withdrawn

382 (not due to adverse event)

	0(0.0)	1(0.6)	1(0.3)
--	--------	--------	--------

383 Other adverse events*

	3(2.0)	2(1.2)	5(1.6)
--	--------	--------	--------

384 Other reasons

	1(0.7)	2(1.2)	3(1.0)
--	--------	--------	--------

385

386 * Tiotropium: cardio-respiratory arrest, chest pain, dry mouth, sudden death

387 Placebo: rash, dry mouth, tremor, nausea and vomiting, constipation, weakness

388

388 Table 3
 389 Trough FEV₁ and FVC response (tiotropium – placebo) for change from baseline
 390 values at 12 weeks by smoking status

	FEV ₁			FVC		
	Difference, LSM (ml)	95% CI	P-value	Difference, LSM (ml)	95% CI	P-value
All patients	102	41, 164	0.0011	164	58, 270	0.0024
Smokers	138	32, 244	0.0105	158	23, 341	0.0870
Ex-smokers	66	3, 129	0.0375	170	62, 278	0.0021

391
 392 LSM, least square means; FEV₁, forced expiratory volume in 1 second; FVC, forced
 393 vital capacity. *Differences between smoking groups were not significant (P=0.6982 for
 394 FEV₁ and P=0.5220 for FVC)
 395

395 Table 4
 396 Adverse event profile

	Tiotropium	Placebo
Patients (n)*	147	164
Serious adverse events	6 (4.1)	3 (1.8)
Patients with adverse events	17 (11.6)	26 (15.9)
Cardiac disorders	2 (1.4)	1 (0.6)
Eye disorders	0 (0.0)	1 (0.6)
Gastrointestinal disorders	3 (2.0)	2 (1.2)
General disorders	6 (4.1)	5 (3.0)
Infections and infestations	1 (0.7)	1 (0.6)
Musculoskeletal and connective tissue disorders	1 (0.7)	2 (1.2)
Nervous system disorders	1 (0.7)	5 (3.0)
Lower respiratory system disorders (excluding exacerbations)	3 (2.0)	6 (3.7)
Exacerbations	6 (4.1)	6 (3.7)
Upper respiratory system disorders	4 (2.7)	4 (2.4)
Skin and subcutaneous disorders	0 (0.0)	1 (0.6)

397 Data are presented as n (%) unless otherwise indicated.

398 *Analysis includes all 311 patients (i.e, including the seven patients who changed their
 399 smoking status during the trial)

400

401 Figure legends

402

403 **Fig. 1.** Mean change in trough FEV₁ during the 12-week study by treatment group and
404 smoking status: (A) smokers and (B) ex-smokers.

405

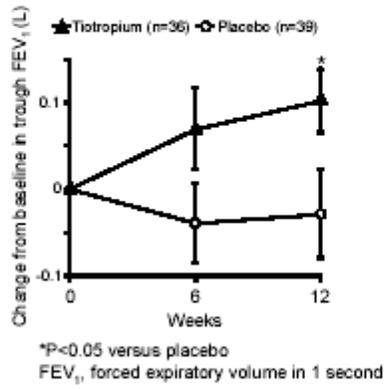
406

407 **Fig. 2.** Mean change (tiotropium–placebo) in daytime rescue medication use in smokers
408 and ex-smokers.

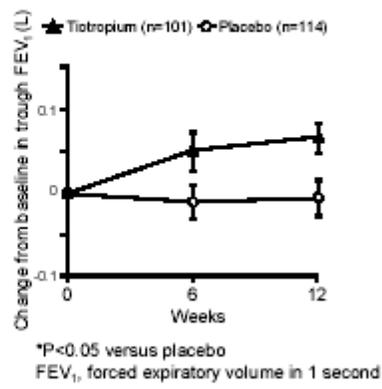
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Figure 1.
A) Smokers



B) Ex-smokers



409

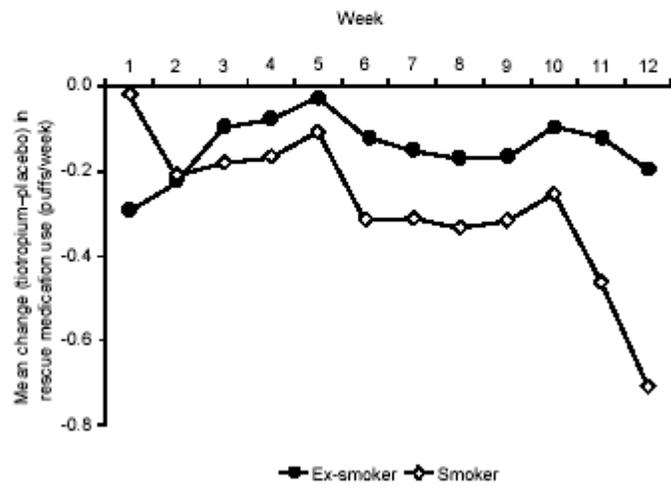
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Figure 2.



411