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# Clinical-functional efficiency of tiotropium bromide in complex treatment of severe persistent asthma patients

**Key words:** *severe persistent bronchial asthma, tiotropium bromidi, inhalative corticosteroid, prolonged $\beta_2$-agonist.*

Presently, utilization of compound preparations including inhaled glucocorticosteroids and prolonged $\beta_2$-agonists are recommended by national and international consensuses to gain control in moderate and severe poorly controlled bronchial asthma (BA) as first line therapy [5, 10, 12, 19, 20].

However, exists a category of patients, in whom clinical, functional and laboratory symptoms of asthma persist, despite of anti-inflammatory therapy using combined medicines [3, 10, 11, 12, 15, 19].

In patients with severe bronchial asthma life quality deteriorates significantly, with high risk of invalidization and treatment, associated with considerable economic costs [3, 5, 9, 11, 18, 21].

The characteristic symptoms of severe BA are: permanent occurrence of daily symptoms, frequent exacerbations, frequent night symptoms, restrictions of physical activity, FEV (forced expiratory volume)$_1$ or PEFR (peak expiratory flow rate) < 60 % of predicted or personally best, PEFR or $FEV_1$ diurnal variability > 30 %, increase of frequency of using of short acting $\beta_2$-agonists (over 8 inhalations within one day), oral GCS administration courses (over 2-3 times a year), as well as frequent emergency ambulance calls [11, 15].

In functional terms, the symptom of severe BA is absence of complete reversibility and fixed bronchial obstruction of various degree of manifestation, accelerated decrease of $FEV_1$, increase of spontaneous or induced bronchial hyperreactivity, $FEV_1$ daily variability, reduction of response to $\beta_2$-agonists [9, 13, 14, 16, 17, 22].

Besides, reduction of lungs elastic response is observed in these patients, which is shown as bronchial tubes collapse and leads to increase of airways resistance of development pulmonary hyperinflation, exasperation of short-breathing and reduction of physical exercise tolerance [15, 16, 17, 18, 22].

This occurs due to the fact that organic changes in the bronchial wall are developed in patients with severe BA, bronchial obstruction is added, and the influence of parasympathetic nervous system becomes stronger [14, 15, 21, 22].

Contents of both eosinophils and neutrophils are increased in the induced sputum in this group of patients, that is, pathophysiological changes which to a greater extent characteristic of chronic obstructive pulmonary disease (COPD) [1, 9, 13, 14, 17, 18].

In this connection, addition of therapeutic regimens used at COPD, in particular, planned therapy with anticholinergic drugs, to baseline therapy may be pathogenically relevant [15, 16, 17, 18, 22].

Anticholinergic drugs block muscarinic receptors of tracheobronchial tree prevent and inhibit endogenous bronchial obstruction stimulated by increased n. Vagus tone, block refractory bronchial spasm related to effect of smoking, industrial and household triggers, reduce secretion of bronchi mucous membrane, reduce pulmonary hyperinflation [4, 7, 8, 11, 20].

Efficiency of using of tiotropium bromide in COPD treatment, based on the evidence-based medicine, a certain similarity of pathophysiologic mechanisms and clinical and functional disorders at COPD and severe BA allowed us to use this medicine in combined complex baseline therapy of patients with severe BA.

*Aim of the study*: to investigate clinical and functional efficiency of complex therapy of severe persisting BA patients using a compound medicine (salmeterol / fluticasone propionate) in combination with tiotropium bromide.

Materials of the study:

30 patients aged 37-75 took part in the study, 12 male and 18 female with stable severe BA, $FEV_1$< 60 % of pred., with positive test of bronchial reversibility. The patients received outpatient treatment in the State institution "Institute of phthisiology and pulmonology at the NAMS of Ukraine".

The 1st group consisted of 7 male and 8 female, their average age (56,3 ± 2,6) years old; average disease duration – (15,9 ± 1,4) year; smoking history (13,7 ± 1,9) "pack/years", the majority quitted smoking immediately after beginning of the disease; $FEV_1$ (43,6 ± 2,8) % of pred.

The 2nd group consisted of 6 male and 9 female, their average age (55,7 ± 2,4) years old; average disease duration – (15,6 ± 1,5) year; smocking history (12,8 ± 1,8) " pack/years"; $FEV_1$ mean value made (48,1 ± 2,8) % of pred.

Upon "washing-out" period during two weeks (fluticasone propionate 125 μg - 2 inhalations (250 μg) 2 twice a day, short actins $\beta_2$-agonists - salbutamol –PRN) the patients were randomized 1:1 for further course of treatment during 2 months.

The patients of the 1st group received during 2 months: salmeterol/fluticasone propionate 50/250 μg and tiotropium bromide (18 μg capsules with powder for inhalations) – one capsule per day.

The patients of the 2nd group received only - salmeterol/fluticasone propionate 50/250 μg - 1 inhalation twice per day.

*The following were under examination:* dynamics clinical symptoms (asthma score, use of b-2-agonists PRN according to self-observation journal); respiratory function indices spirometry with analyzis the forced expiration "flow-volume" curve and whole-body plethysmography (on the "MasterLab" apparat, "Erich Jaeger"), respiratory muscles strength ("MasterScope", "Erich Jaeger"); Peak flow meter ("Vitest").

*Results:* according to analysis of the self-observation journals, the number of night symptoms reduced reliably ($p < 0,01$) in patients of the 1st group vs to the baseline data — from (1,99 ± 0,06) to (0,82 ± 0,06); morning chest tightness — from (1,63 ± 0,07) to (0,73 ± 0,05); the number of daily symptoms — from (2,35 ± 0,06) to (1,19 ± 0,06); cough — from (1,86 ± 0,05) to (1,01 ± 0,08); dyspnoe score — from (3,3 ± 0,3) to (1,5 ± 0,3). Need rescue medication reduced reliably ($p < 0,01$) from (3,9 ± 0,6) in the beginning to (1,5 ± 0,2) times after the course of treatment (figure 1).

In the 2nd group of patients, the following were reliably ($p < 0,01$) reduced in the course of treatment: night symptoms — from (1,91 ± 0,13) to (1,46 ± 0,11); daily symptoms — from (1,91 ± 0,11) to (1,39 ± 0,10); dyspnoe score — from (1,8 ± 0,2) to (1,2 ± 0,2). Other indicators — morning chest tightness, cough during the day, as well as the number of $b\text{-}_2$-agonists inhalations only had a tendency to reduction. The dynamics of clinical symptoms in patients of the 2nd group based on the data of self-observation journals is represented on figure 2.

Analysis of the obtained data demonstrated that reliable ($p < 0,05$) inspiratory capacity increase was observed in patients of the 1st group as compared with patients of the 2nd group (by 44,2 %), as well as more expressed but not reliable reduction of the residual volume and functional residual lung capacity.

A positive dynamics among the bronchial permeability indicators was also observed in patients of the 1st group. Thus, by the end of the 1st month of treatment, $FEV_1$ reliably ($p < 0,05$) increased vs baseline: from (42,4 ± 4,1) % to (52,1 ± 3,7) % and even to a greater extent upon termination of the treatment course – to (59,3 ± 4,8) %. The following factors increased statistically reliable ($p < 0,05$) as compared baseline data: $FEF_{50}$ from (22,2 ± 3,2) % to (33,7 ± 4,0) % upon the 1st month of treatment and to (37,5 ± 5,4) % upon termination of the treatment course, $FEF_{25}$ – from (21,5 ± 2,0) % to (33,2 (3,8) % ($p < 0,05$) upon the 1st month and to (36,2 (4,1) % ($p < 0,05$) upon the end of the study, bronchial permeability on the level of 75-85 % of the forced vital lung capacity by the end of the first month of treatment increased by 60 %, and upon ter-

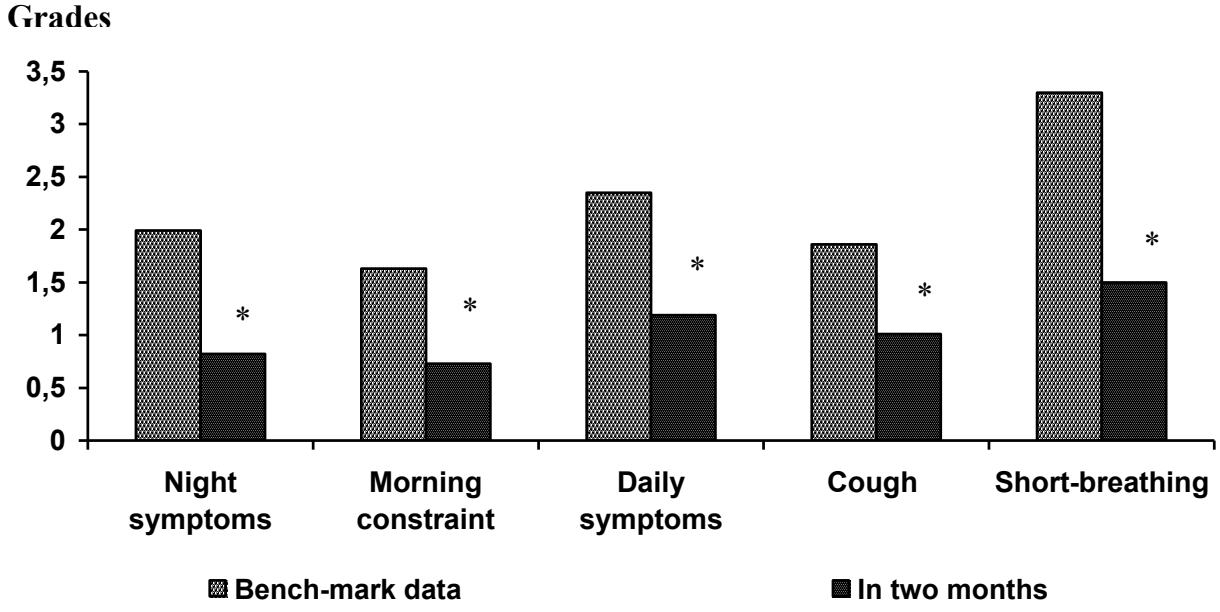


***Figure 1*** **Dynamics of BA clinical symptoms in patients of the 1st group.**

* $p < 0,01$ as compared to the baseline data.

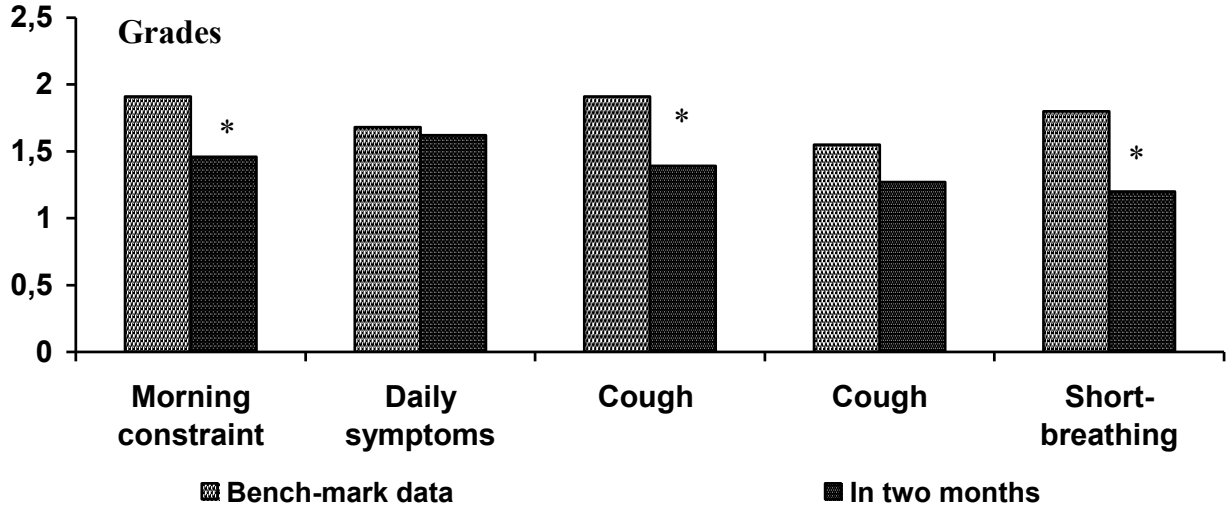


***Figure 2*** **Dynamics of BA clinical symptoms in patients of the 2nd group.**

* p < 0,01 as compared to the baseline data.

mination of the treatment course under consideration – virtually twice (figure 3).

$FEV_1$/FVC also changed (p < 0,05) in two months of treatment from (59,0 ± 1,1) to (77,2 ± 1,4) %.

Statistically valueless dynamics of main respirometry indices was observed in patients of the 2nd group. Thus, forced expiratory volume for the first second, indicators of permeability on the level of medium bronchi and bronchial tubes increased slightly.

The data obtained testify to the fact that addition of tiotropium bromide to the complex anti-inflammatory therapy salmeterol/fluticasone propionate combination in severe persisting BA patients during 2 months of was more efficient regimen, compared to the salmeterol/fluticasone propionate combination:

1. More expressed and earlier reduction of asthma symptoms, need of rescue medication.
2. Significant improvement of bronchial permeability - reliable increase of $FEV_1$, $FEV_1$/FVC, $FEF_{50}$, $FEF_{25}$, $FEF_{25-75}$.
3. Reduction of pulmonary hyperinflation, which was confirmed by a reliable increase of inspiratory capacity, reduction of functional residual lung capacity and residual volume.

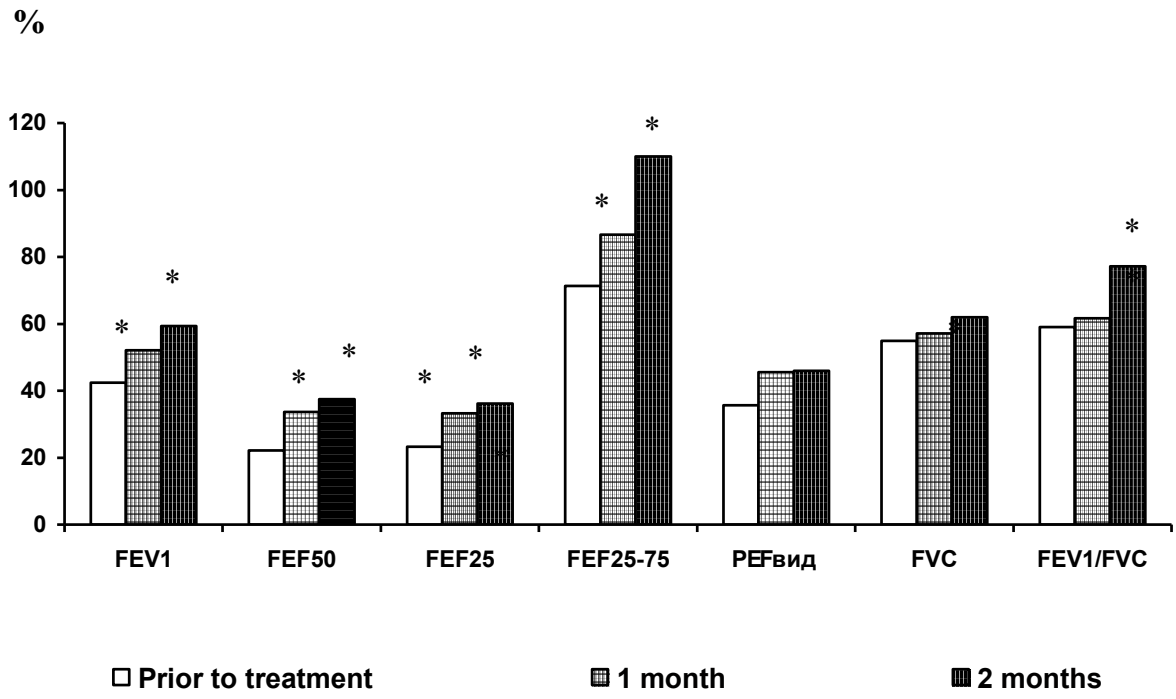


***Figure 3*** **Salmeterol/ fluticasone propionate and tiotropium bromide effect on bronchial permeability indicators in patients of the 1st group.**

* p < 0,01 as compared to the baseline data.

Thus, addition of tiotropium bromide to the combination of ICS and $\beta_2$-agonists of prolonged action is pathogenically justified, allows significantly reducie symptoms, need of rescue medication, improving respiratory function and optimizing control over the disease in severe BA patients.

## References


1. *Ільїнська, І. Ф.* Визначення поглинальної здатності фагоцитуючих клітин індукованого харкотиння у хворих з бронхо-легеневими захворюваннями для здійснення їх моніторингу та оцінки ефективності лікування [Текст] / І. Ф. Ільїнська, Ю. О. Матвієнко, Л. В. Ареф'єва // Лабораторна діагностика. – 2006. – № 4. – С. 26–30.

2. *Лапач, С. Н.* Статистические методы в медико-биологических исследованиях с использованием Excel [Текст] / С. Н. Лапач, А. В. Чубенко, П. Н. Бабич. – К. : Морион, 2001. – 408 с.

3. *Наказ* МОЗ України від 19.03.2007 р. № 128 «Про затвердження клінічних протоколів надання медичної допомоги за спеціальністю "Пульмонологія"». – К., 2007. – 146 с.

4. *Перцева, Т. О.* Досвід застосування спіриви (тіотропію броміду) у хворих на хронічне обструктивне захворювання легень [Текст] / Т. О. Перцева, Л. І. Конопкіна, О. В. Мироненко // Укр. пульмонол. журн. – 2005. – № 3. – С. 32–34.

5. *Фещенко, Ю. И.* Бронхиальная астма - одна из главных проблем современной медицины [Текст] / Ю. И. Фещенко // Укр. пульмонол. журн. – 2000. – № 2 (додаток). – С. 13–15.6. *Фещенко, Ю. И.* Основные принципы лечения бронхиальной астмы [Текст] / Ю. И. Фещенко // Укр. пульмонол. журн. – 2000. – № 2 (додаток). – С. 22–25.

7. *Фещенко, Ю. І.* Сучасний підхід до фармакотерапії бронхіальної астми [Текст] / Ю. І. Фещенко // Мистецтво лікування. – 2003. – № 4. – С. 6–12.

8. *Фещенко, Ю. І.* Основи інгаляційної терапії при хронічному обструктивному захворюванні легень та бронхіальній астмі: Посібник для лікарів [Текст] / Ю. І. Фещенко, Т. О. Перцева, Л. І. Конопкіна. – К. : Книга, 2005. - 86 с.

9. *Фещенко, Ю. І.* Схожість та відмінність бронхіальної астми та ХОЗЛ [Текст] / Ю. І. Фещенко, Л. О. Яшина // Нова медицина. – 2006. – № 1. – С. 20–22.

10. *Яшина, Л. А.* Достижение контроля бронхиальной астмы – современная стратегия ведения заболевания [Текст] / Л. А. Яшина // Здоров'я України. – 2008. – № 3/1. – 10 с.

11. *Яшина, Л. А.* Методологический подход к диагностике и лечению трудной, терапиерезистентной бронхиальной астмы [Текст] / Л. А. Яшина // Астма та алергія. – 2002. – № 1. – С. 71–76.

12. *Яшина, Л. А.* Астма-контроль [Текст] / Л. А. Яшина // Укр. пульмонол. журн. – 2003. – № 2. – С. 13–18.

13. *Airway* structural alterations selectively associated with severe asthma [Text] / Benayoun L. [et al.] // Am. J. Respir. Crit. Care Med. – 2003. – Vol. 167. – P. 1360–1368.

14. *Barnes, P. J.* Parameters associated with persistent airflow obstruction in chronic severe asthma [Text] / P. J. Barnes, D. Robinson, K. F. Chung // Eur. Respir. J. – 2004. – Vol. 24. – P. 122–128.

15. *Barnes, P. J.* Introduction: how can we improve asthma management? [Text] / P. J. Barnes // Current medical research and opinion. – 2005. – Vol. 21, Suppl. 4. – P. 1–3.

16. *Beckett, P. A.* Pharmacotherapy and airway remodelling in asthma? [Text] / P. A. Beckett, P. H. Howarth // Thorax. – 2003. – Vol. 58. – P. 163–174.

17. *Benayoun, L.* Airway structural alterations selectively associated with severe asthma [Text] / L. Benayoun, A. Druilhe, M. Dombret // Am. J. Respir. Crit. Care Med. – 2003. – Vol. 167. – P. 1368.

18. *Bell, E. H.* Severe asthma [Text] / E. H. Bell // Breathe. – 2006. – Vol. 3. – P. 129–138.

19. *Global* Strategy for Asthma Management and Prevention // National Institutes of Health National Heart & Lung and Blood Institute. – 2007. – 96 p.

20. *The Global* initiative for asthma (GINA) 2013 [Электронный ресурс]. – Режим доступа: http//www.ginasthma.org/pdf/GINA_Report_2013.pdf.

21. *Wenzel, S.* Severe asthma in adults [Text] / S. Wenzel // Am. J. Respir. Crit. Care Med. – 2005. – Vol. 177. – P. 149–160.

22. *Wenzel, S.* Mechanisms of severe asthma [Text] / S. Wenzel // Clinical Experimental Allergy. – 2003. – Vol. 33. – P. 1622–1628.


### КЛІНІКО-ФУНКЦІОНАЛЬНА ЕФЕКТИВНІСТЬ ТІОТРОПІЮ БРОМІДУ В КОМПЛЕКСНОМУ ЛІКУВАННІ ТЯЖКОЇ ПЕРСИСТУЮЧОЇ БРОНХІАЛЬНОЇ АСТМИ

*С. М. Москаленко*

**Резюме.** *На сьогоднішній день, незважаючи на проведення терапії хворим на тяжку персистуючу бронхіальну астму (БА), рекомендованої національними та міжнародними узгодженнями, не вдається досягти контрольованого перебігу захворювання у певної частини хворих. Проведено вивчення ефективності лікування із застосуванням пролонгованого холінолітика тіотропію броміду в комплексному лікуванні хворих на тяжку БА. Показано, що додавання тіотропіуму броміду зумовлює позитивні зміни клінічних симптомів, покращення функції зовнішнього дихання, зменшення гіперінфляції та ознак запального процесу. Запропоновано спосіб лікування із додаванням тіотропію броміду до середніх доз інгаляційних кортикостероїдів в комбінації з пролонгованим $\beta_2$-агоністом у комплексній базисній терапії хворих на тяжку БА.*

**Ключові слова:** *тяжка персистуюча бронхіальна астма, тіотропію бромід, інгаляційний кортикостероїд, $\beta_2$-агоніст пролонгованої дії.*

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### CLINICAL-FUNCTIONAL EFFICIENCY OF TIOTROPIUM BROMIDI ON COMPLEX TREATMENT OF SEVERE PERSISTENT ASTHMA

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**Summary.** *Although the majority of asthma patients can obtain the acceptable level of control some severe asthma patients will not do so even with the standart therapy, recommended by national and international guidelines. The dissertation is dedicated to the study of effectiveness of use of prolonged cholynolytic tiotropium bromidum in complex basic therapy in severe asthma patients. It was shown, that addition of tiotropium bromidum leads to the positive changes in clinical symptoms, improvement in indices of function, decrease of hyperinflation and signs of inflammation. Suggested new method of treatment with addition of tiotropium bromidum to the medium doses of inhalative steroides combined with prolonged $\beta_2$-agonis in complex basic therapy in severe asthma patients.*

**Key words:** *severe persistent bronchila asthma, tiotropium bromidum, inhalative corticosteroid, prolonged $\beta_2$-agonist.*

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