Efficacy of pharmacological methods used for treating tobacco dependence: meta-analysis

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Abstract: Objectives. The present study summarizes available evidence describing efficacy of pharmacological methods used in smoking cessation and presents the results of new meta-analyses examining their 12-month efficacy. This work represents part of a larger program examining the efficacy and cost-effectiveness of different methods used in smoking cessation. **Patients and methods.** The first part of the study included systematic review of literature to identify methods used in smoking cessation with efficacy confirmed on the basis of existing reliable systematic reviews or meta-analyses. In the second stage of the process, for the interventions judged both available in Poland (on the basis of literature search and interviews with healthcare providers) and efficacious, we have performed new meta-analyses designed to establish their 12-month efficacy (continuous or prolonged abstinence). **Results.** We found that the most comprehensive and up-to-date data were available in Cochrane reviews. Meta-analyses of randomised controlled trials performed in the second part of the work showed that adding pharmacological methods of smoking cessation available in Poland, such as nicotine replacement therapy (NRT) and bupropion, to nonpharmacological methods increased the probability of smoking cessation and smoking abstinence for ≥12 months by over 1.5 to about 3 times and the number needed to treat to have one patient stop smoking ranged from 8 to 21. **Conclusions.** We confirmed that pharmacological methods of smoking cessation available in Poland, such as NRT and bupropion, added to nonpharmacological methods increase the probability of smoking abstinence and we quantified 12-month effects of these interventions.

Key words: bupropion, meta-analysis, nicotine replacement therapy, tobacco dependence, treatment efficacy

INTRODUCTION

Tobacco dependence is a disease specified in the 10th Revision of International Classification of Diseases [1]. A half of long-term smokers are estimated to die due to tobacco dependence with 50% of these cases in a productive age. Tobacco use is a predominant risk factor for lung cancer, as well as cardiovascular and respiratory system diseases [2-4]. Available data in 1990 for the Polish population of 35–69 years showed that 91% of lung cancer cases in men and 65% in women, 58% of all cancer cases in men and 8% in women and 42% of cardiovascular diseases in men and 11% in women as well as 71% of respiratory diseases in men and 36% in women, were directly caused by smoking [5].

At present 34% of men and 22% of women in Poland are smokers [5]. Estimates show that annual expenditures on treatment of smoking related diseases in Poland amount to 18 billion PLN [6], and if a prevalence of smoking does not change, the direct cost of treatment within 20 years will reach 198 billion PLN [7].

Smoking cessation brings substantial health benefits. A systematic review of 20 prospective cohort studies showed that smoking cessation, even among subjects with already diagnosed ischemic heart disease, is associated with a reduction in risk of death from any cause (relative risk [RR] 0.64, 95% CI 0.58–0.71), as well as in the risk of recurrent myocardial infarction (RR 0.68, 95% CI 0.57–0.82) [8]. Reduction in the risk of death from any cause associated with smoking cessation in patients with ischemic heart disease is more pronounced than that associated with any other secondary prophylaxis intervention: β-blockers (OR 0.77, 95% CI 0.57–0.85) [9] or angiotensin converting enzyme inhibitors (OR 0.8, 95% CI 0.74–0.87) [10].

Reduction in smoking prevalence in Poland by introducing the interventions of confirmed efficacy into tobacco dependence treatment may result in the reduction in morbidity and mortality due to smoking related diseases, thus in cost reduction.

Identification of methods used for tobacco dependence treatment based on systematic review and their efficacy analy-

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Table 1. Tobacco dependence treatment methods which efficacy was assessed in systematic reviews or meta-analyses found

Intervention	Number of systematic reviews/meta-analyses (years of publication)	Cochrane review, last search
Nicotine replacement therapy	9 (1987–2004) [12–20]	March 2004 [18][a]
Bupropion	3 (2002–2004) [20–22]	March 2004 [21][a]
Clonidine	2 (1991–2004) [23,24]	May 2004 [24][a]
Nortriptiline	1 (2004) [21]	the only review; March 2004 [21]
Other antidepressants	1 (2004) [21]	the only review; March 2004 [21]
Anxiolytics	1 (2000) [25]	the only review; August 2003 [25]
Opioid agonists	1 (2001) [26]	the only review; March 2001 [26]
Lobeline	1 (1997) [27]	the only review; May 1997 [27]
Mecamylamine	1 (1998) [28]	the only review; February 2002 [28]
Citizine	none	none

[a] The most complete and up-to-date search

sis based on reliable scientific research will make it possible to determine which of them could be of benefit and should be applied on a wider scale.

The objective of the study was to assess the efficacy and cost-effectiveness of methods used in the tobacco dependence treatment. The current report deals only with analysis of efficacy of pharmacological methods used in smoking cessation.

PATIENTS AND METHODS

The detailed description of methodology was presented in the previous paper [11]. In brief, the study presented included 2 phases:

1. Systematic review of data to identify pharmacological methods of smoking cessation treatment and preliminary efficacy evaluation on the basis of existing reliable systematic reviews and meta-analyses of randomized trials (abstinence after at least 6 months from the start of treatment). Twenty-five electronic databases were searched i.a. CINAHL, EMBASE, MEDLINE, via PubMed, ProQuest, PsycINFO for the period until March 2004 and Cochrane Library in January 2005. Search was limited to studies performed in adults. The efficacy of the identified methods in increasing of the probability of abstinence was assessed on the basis of existing reliable systematic reviews and meta-analyses. To be included in further analysis an intervention was required to have its efficacy i.e. a significant difference in the percentage of individuals remaining in continuous abstinence after at least 6 months from the beginning of therapy, shown in a reliable systematic review or meta-analysis. The results of all the reviews were summarized, and the most up-to-date reliable systematic reviews were selected for further analysis.

2. Availability of individual tobacco dependence treatment methods in Poland was defined based on the available data and interviews with health service providers. Original studies, where the treatment efficacy was expressed as 12-month, continuous or prolonged tobacco abstinence [see below] (irrespective of the year of the study publication and the number of persons subjected to intervention) were extracted from reliable systematic reviews and meta-analyses, which were used for initial efficacy assessment; the studies, where abstinence was assessed only during the week preceding the medical control, were excluded.

In the next stage, meta-analysis of data from those studies was performed and their impact on achieving at least a 12-month continuous abstinence (refraining from smoking from the moment of smoking cessation for the period of 12 months; occasional slips/lapses are possible) or prolonged abstinence (refraining from smoking from the moment of smoking cessation for 12 months; during the first two weeks from the target date of smoking cessation, isolated lapses are possible) was defined. Application of data concerning the 12-month abstinence was associated with the fact that the available epidemiological data (risk of death and risk of disease) used in cost-effectiveness analysis and an economic model cover 12-month periods. Moreover, tobacco abstinence lasting at least one year provides a good chance of total success. The data for meta-analysis were extracted from primary studies included in the analysis.

RESULTS

In Table 1 there are listed systematic reviews and meta-analyses assessing the efficacy of pharmacological tobacco dependence treatment methods that were found during the first stage of the study.

The most complete and up-to-date data were included in the reviews made in accordance with Cochrane Collaboration methodology.

During the study, among the pharmacological treatment methods, whose efficacy was unambiguously confirmed, the following were available in Poland: bupropion and nicotine

replacement therapy (nicotine gum, transdermal patches, lozenge – approved and available; inhaler and nasal spray – approved but unavailable).

1. Nicotine replacement therapy (NRT)

Available reviews

Nine meta-analyses and systematic reviews were found published in 13 papers from 1987 to 2004. In 2 of those efficacy of nicotine gum alone was assessed [12,16] and its efficacy in tobacco abstinence comparing to no nicotine gum was shown, especially if provided in specialized centers (27% vs. 18% [16]).

In three papers efficacy of nicotine transdermal patch alone was assessed [13,14,17] and its efficacy comparing to placebo was shown (OR 3.0 [13]; OR 2.3, 95% CI 1.6–3.4 [14]; OR 2.26 [17]).

Similar results were obtained in 2 reviews assessing nicotine gum and transdermal patches efficacy in patients treated in therapeutic program or according to medical advice (nicotine gum – risk difference [RD] 6%, 95% CI 4–8%; transdermal patches – RD 9%, 95% CI 6–13% [19]), as well as without any medical advice or as over-the-counter (OTC) drugs (OR 2.5, 95% CI 1.8–3.6) [15].

In the HTA report assessing NRT and bupropion efficacy [20] and in Cochrane review, first published in 1994, continuosly updated [18], all the NRT methods were assessed. Probability of continuous abstinence for 6 months comparing with non-NRT treatment was shown to be significantly higher (OR 1.72, 95% CI 1.61–1.84 [20]; OR 1.75, 95% CI 1.64–1.87 [18]).

Commonly observed adverse events for nicotine gum treatment were: hiccup, gastro-intestinal symptoms, jaw pain, tooth and periodontal diseases; for transdermal patches – mild dermatitis (25% vs. 13%); and sublingual tablets – hiccup, feeling of burning or smarting sensation in the mouth, sore throat, dryness of lips and mouth ulcers [18,20]. Serious adverse events and adverse events resulting in study withdrawal were equally frequent in NRT group and control (4% vs. 2.5%) [20]. In the review regarding adverse events of transdermal patches, that included 35 studies, a low occurrence of cardiovascular symptoms was shown, not increased compared with the control group (myocardial infarction 1% vs. 1%; stroke 0.3% vs. 1%; angina 0.4% vs. 0.4%, arrhythmia 3% vs. 2%, hypertension 2% vs. 1%) [18,20,29]. The observation provided by FDA showed that adverse effect occurrence is 12.3/million of patients for nicotine gum and 11.8/million for transdermal patches [20].

Efficacy analysis in achieving the 12-month abstinence

In the Cochrane review the most up-to date efficacy data were included; the last search was performed in 2004. The references of papers included were compared with references of papers included to the remaining reviews/meta-analyses.

From among 103 papers incorporated in Cochrane systematic review [18], 50 were included in efficacy analysis, which assessed the effect of NRT added to simple advice, individual counseling or group therapy, on abstinence for 12 month (see appendix). All of those were randomized trials with control group not receiving NRT. In 29 studies efficacy of nicotine gums, in 19 – transdermal nicotine patches and in 2 – nicotine lozenge was assessed (see appendix).

The results of primary studies included in efficacy analysis were pooled by means of meta-analysis, and significant benefits of NRT use were observed:

- in combination with simple advice – relative benefit increase (RBI) 64% (16 studies, Tab. 2, Fig. 1),
- in combination with individual counseling – RBI 52% (19 studies, Tab. 2, Fig. 2),
- in combination with group therapy – RBI 63% (15 studies, Tab. 2, Fig. 3).

2. Bupropion

Available reviews

Efficacy of bupropion in comparison with the control group receiving placebo and individual counseling or group therapy, was confirmed in 3 reviews and meta-analyses published between 2002–2004 (OR 2.75, 95% CI 1.98–3.81 [20]; 23–35% vs. 12–16%, $p < 0.05$) [22]; OR 2.06, 95% CI 1.77–2.4 [21]).

The commonly observed adverse events of bupropion treatment were insomnia (30–40% vs. 20%), mouth dryness 10–13% vs. 4.5%) and nausea [21,30]. Symptoms that caused withdrawal from the study were observed in 5–12% of patients receiving bupropion as compared with 4–8% of patients receiving placebo [20]. Treatment with bupropion may be associated with seizures (1/1,000 patients receiving bupropion in an open, non-controlled trial; similar occurrence in national registry of adverse events and clinical trials), allergic reactions – itching, allergic dermatitis, angioedema, dysponea (1–3/1000 in clinical trials and national registry of adverse events) [20,21]. In observational trials after the drug was launched, the symptoms of joint pain, muscle pain, fever and rash were reported, serum sickness-like symptoms (less than 1/1000) and suicidal thoughts (1/667 in clinical trials, 1/10,000 in national registry of adverse events) [20,21]. In the safety assessment provided by the European Agency for the Evaluation of Medicines for Human Use [21,31], occurrence of suicidal thoughts during bupropion therapy is mentioned to be low as compared to the general population, but no data was shown. The Agency recommended placing a warning message about possible hyper reactivity and depression in the drug information leaflet. According to the Agency, the benefits outweigh the harm observed during therapy with bupropion.

Efficacy analysis in achieving the 12-month abstinence

In the Cochrane review [21] the most up-to date efficacy data were included; the last search was performed in 2004.

Table 2. Efficacy of individual pharmacological tobacco dependence treatment methods in achieving a 12-month abstinence

Method	Treatment (%) (95% CI)	Control (%) (95% CI)	Relative benefit (95% CI)	Benefit difference (95% CI)	NNT (95% CI)
Bupropion added to individual counseling vs. individual counseling and placebo	17.5 (15.9–19.1)	10.1 (8.5–11.7)	1.74 (1.45–2.09)	0.075 (0.05–0.10)	14 (11–20)
Bupropion added to group therapy vs. group therapy and placebo	18.4 (12.9–23.9)	6.5 (3.0–10.0)	2.85 (1.53–5.3)	0.12 (0.06–0.18)	9 (6–18)
NRT added to simple advice vs. simple advice	12.9 (12.0–13.8)	7.8 (7.1–8.6)	1.64 (1.45–1.87)	0.05 (0.038–0.063)	20 (16–27)
NRT added to individual counseling vs. individual counseling	14.3 (13.3–15.2)	9.4 (8.6–10.2)	1.52 (1.35–1.70)	0.048 (0.036–0.061)	21 (17–28)
NRT added to group therapy vs. group therapy	33.3 (30.5–36.1)	20.4 (18.0–22.8)	1.63 (1.41–1.88)	0.13 (0.09–0.16)	8 (7–11)
Bupropion + NRT added to individual counseling vs. individual counseling	22.4 (17.4–28.2)	5.6 (2.6–10.4)	3.99 (2.08–7.8)	0.17 (0.11–0.23)	6 (5–10)

NNT – number needed-to-treat, NRT – nicotine replacement therapy

The references of papers included were compared with references of papers included to remaining reviews/meta-analyses.

From among 24 papers incorporated in the systematic review [21], 11 were included in efficacy analysis which assessed the effect of bupropion added to individual counseling or group therapy, on abstinence for 12 months (see appendix). All of those were randomized trials with control groups receiving individual counseling or group therapy and placebo.

The results of primary studies included in efficacy analysis were pooled by means of meta-analysis, and significant benefits were observed:

– of bupropion added to individual counseling compared with counseling and placebo – RBI 74% (8 studies, Tab. 2, Fig. 4)
– of bupropion added to group therapy compared with group therapy and placebo – RBI 185% (3 studies, Tab. 2, Fig. 5). However, the patient groups in those studies were small, in one of those in the control group no one stopped smoking, therefore confidence intervals for that treatment effect are wide.

3. Bupropion together with NRT

Bupropion used along with NRT comparing with placebo was assessed in one trial (together with individual counseling in both groups) [21,32]. A significant benefit was observed (Tab. 2). However, this result was obtained from 1 study with low precision.

4. Other pharmacological methods used for treating tobacco dependence

Moreover, unambiguous data confirming efficacy in achieving abstinence with clonidine use (OR 1.89, 95% CI 1.30–2.74) [24], which is not approved for treating tobacco dependence in Poland and nortriptyline (OR 2.79, 95% CI 1.70–4.59) [21], which is not available in Poland were found. Therefore they were not taken into consideration in efficacy analysis of achieving the 12-month abstinence.

In the systematic reviews or meta-analyses we found the efficacy of the following methods was not confirmed:

– antidepressants other than bupropion and nortriptyline [21]
– anxiolytics [25]
– opioid antagonists [26]
– lobeline[27]
– mecamylamine [28].

No randomized studies for cytyzine were found [33,34].

DISCUSSION

In the studies included in the meta-analysis 1 year, probability of abstinence ranges between 0% and 38.5% in control groups, 8.8% and 43% in bupropion group and 3.1% and 52.4% in the NRT group. Estimated abstinence rate was in controls 5.6–20.4% and in treated groups – 12.9% for NRT to 33.3% for bupropion.

In the systematic reviews analysis and in a meta-analyses of randomized trials concerning pharmacological methods of tobacco dependence treatment, the efficacy of methods available in Poland i.e. bupropion and nicotine replacement therapy in increasing a 12-month probability of tobacco abstinence was confirmed. Adding bupropion was associated with a 2-fold increase of probability of smoking cessation and abstinence for 12 months comparing with individual counseling alone and about 3 fold increase compared to the group therapy alone with number need to treat (NNT) 14 and 9, respectively.

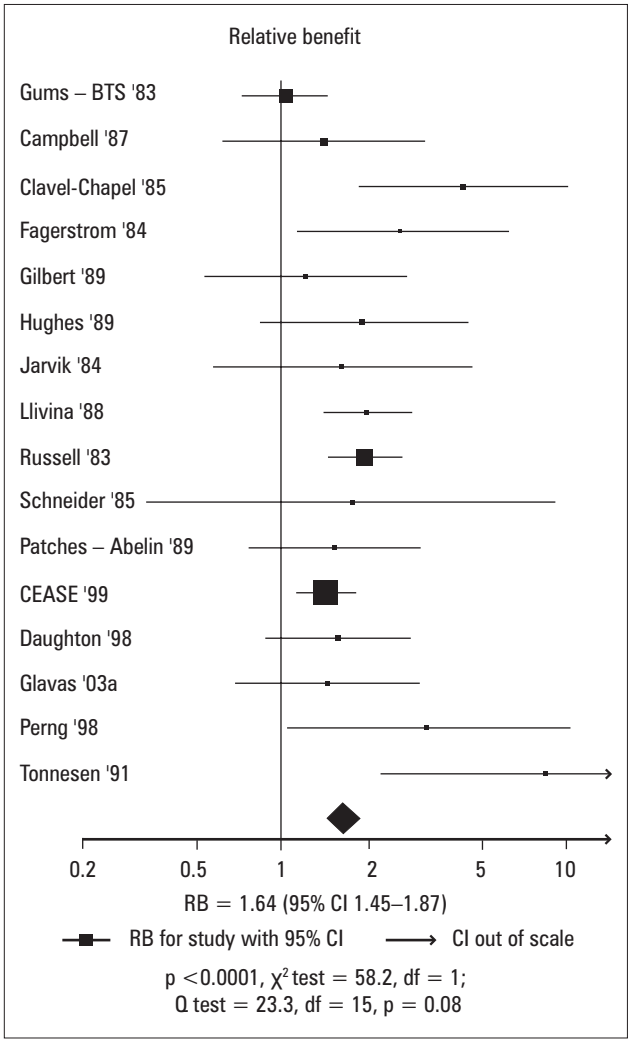

Fig. 1. Efficacy of nicotine replacement therapy added to simple advice in achieving 12-month abstinence – relative benefit (RB) vs. simple advice alone. References – see appendix

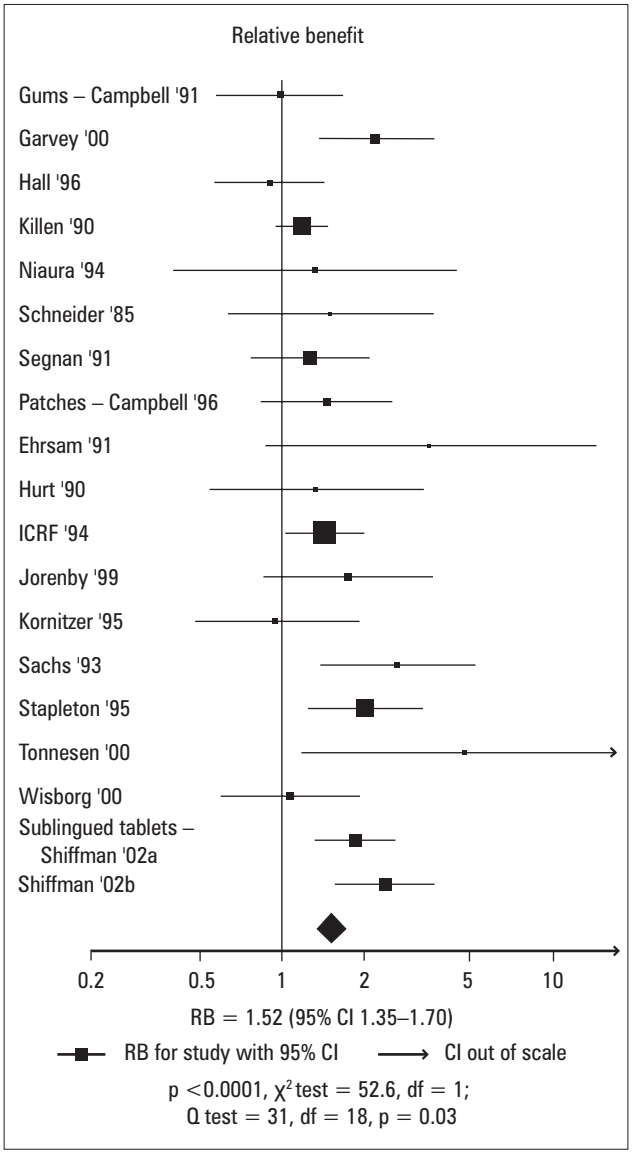

Fig. 2. Efficacy of nicotine replacement therapy added to individual counseling in achieving 12-month abstinence – relative benefit (RB) vs. individual counseling alone. References – see appendix

Adding of NRT to simple advice (short intervention lasting ≤10 min with at most 1 control visit), individual counseling or group therapy, increased the probability of smoking cessation about 1.5 times comparing with the respective control group with NNT 8–21. Moreover, adding NRT together with bupropion to individual counseling increased that probability about 4 times with NNT 6. However, the value of these data should not be overestimated because it comes from one randomized study with a wide confidence interval for relative benefit (95% CI 2.08–7.8).

When the analysis was performed, the only available methods of NRT in Poland were nicotine gums, transdermal patches and lozenges. However, lately, also inhalers and sublingual tablets become available. According to Cochrane review meta-analyses, those methods increase the probability of smoking cessation in at least 6 months observation similar to other methods – about 2 times (OR for inhalers: 2.14, 95% CI 1.44–3.18; OR for lozenges and sublingual together: 2.05, 95% CI 1.62–2.59) [18].

The results presented are consistent with results of other studies and with recommendations regarding treatment of tobacco dependence which mention bupropion and nicotine replacement therapy as a first-line treatment [35-38].

During the current search none of randomized trials with citizine, the medication available in Poland for 40 years, was found. However, authors of systematic review published in 2007 [39], which assessed the efficacy of partial nicotine receptor agonists, found a randomized study of poor quality, performed in the early 1970 in a single nicotine dependence treatment center in East Germany [40]. The abstinence according to the patient report was

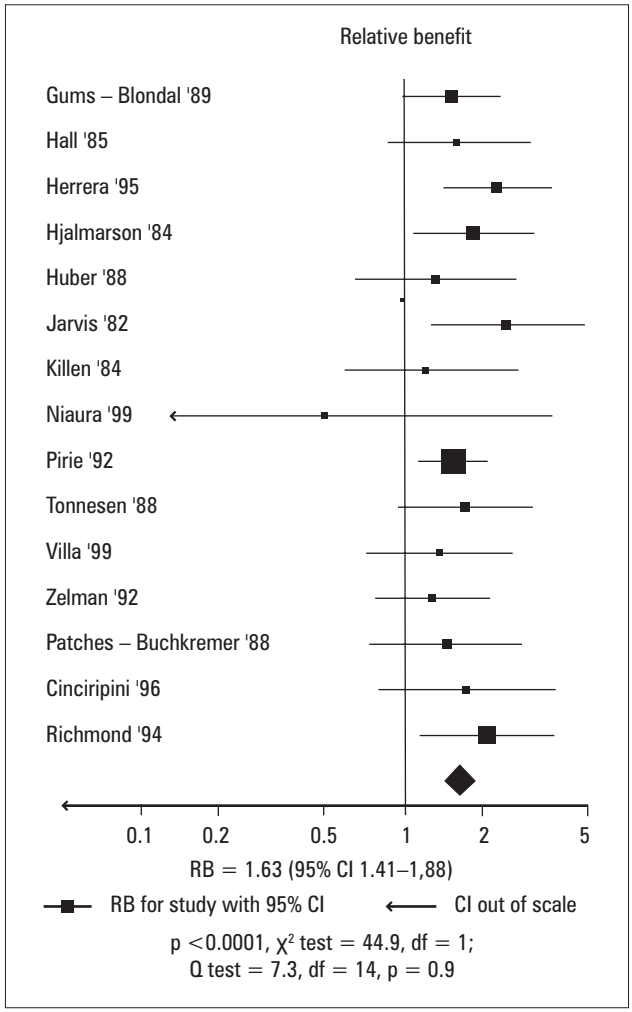

Fig. 3. Efficacy of nicotine replacement therapy added to group therapy in achieving 12-month abstinence – relative benefit (RB) vs. group therapy alone. References – see: appendix

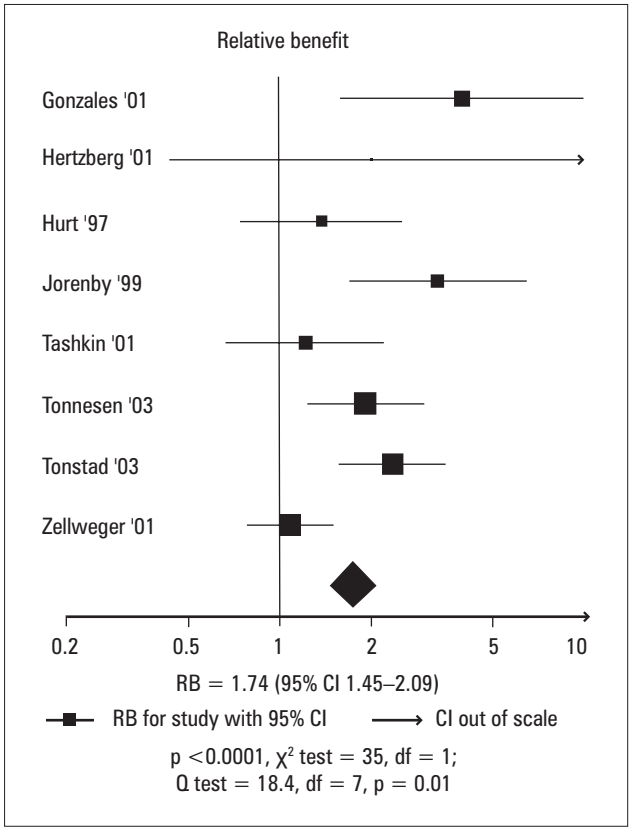

Fig. 4. Efficacy of bupropion therapy added to individual counseling in achieving 12-month abstinence – relative benefit (RB) vs. individual counseling alone. References – see appendix

assessed after 4 weeks, 6 months and 2 years of treatment. The probability of smoking cessation in the citizine group compared with placebo increased more than 1.5 times (OR 1.77, 95% CI 1.3–2.4). At present there is a randomized clinical trial ongoing in Poland with the purpose of citizine efficacy assessment [41]. On the basis of citizine the varenicline, partial nicotine receptor agonist was developed, which was launched in Poland in 2007. Its efficacy in increacing the probability of 12 month abstinence was confirmed in 5 randomized studies (OR 3.22, 95% CI 2.43–4.27). In 3 of these studies more patients stopped smoking and remained abstinent for 12-months in the varenicline group than in the bupropion group (OR 1.66, 95% CI 1.28–2.16) [39]. In the recent recommendations of the European Respiratory Society regarding tobacco dependence treatment in patients with respiratory diseases, varenicline was mentioned as a second-line treatment [37].

Clinical studies confirmed that smoking cessation is associated with mortality and morbidity risk reduction due to tobacco related diseases [8,42-44]. In analyses performed in other countries different methods of smoking cessation support were found cost-effective. The cost effectiveness of smoking cessation supporting interventions is much more pronounced than in the majority of medical interventions at all levels of medical care [45]. However despite that, those interventions are often not refunded by health care providers. According to some authors, NRT and bupropion are one of the most cost effective interventions in health care system [46]. In the study assessing 500 life-saving interventions the median of costs was 42,000 USD per life year gained (1993) with the majority of widely used interventions costing 100,000 USD per life year gained. Compared with that: in European studies incremental cost effectiveness (the additional cost for the additional health effect) of different NRT added to medical counseling is 3113–6879 EUR per life year gained in male and 3779–8799 EUR per life year gained in female [47]; moreover, if bupropion was added to individual counseling the incremental cost per life year gained was estimanted in one study to be 639–1278 GBP [20], an id the another 1,768–2,851 EUR in male and 2146–3646 EUR in female [47].

The reimbursement of tobacco dependence treatment may be an interventia increasing probability of smoking cessation

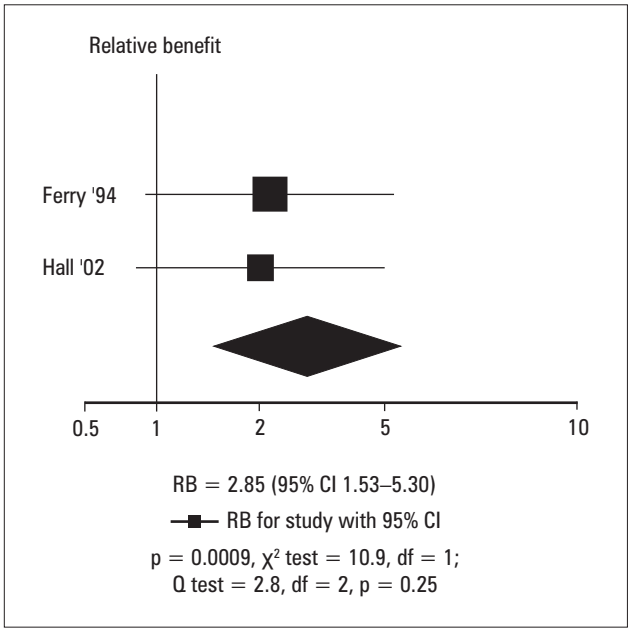

Fig. 5. Efficacy of bupropion therapy added to group therapy in achieving 12-month abstinence – relative benefit (RB) vs. group therapy alone. References – see appendix

by itself. Cochrane systemic review [48] showed that, comparing to partial or no reimbursement, the total treatment cost reimbursement may increase a probability of the abstinence for at least 6 months (OR 1.48, 95% CI 1.17–1.88), the probability of smoking cessation attempt (OR 1.32, 95% CI 1.18–1.49), use of pharmacologic substances supporting smoking cessation (for NRT: OR 2.92, 95% CI 1.49–5.71; for bupropion: OR 2.47, 95% CI 0.85–7.13) and non-pharmacological methods (OR 3.67, 95% CI 3.06–4.39). However, the differences between groups were not significant and poor study methodology require caution in the interpretation of the review results. The cost-effectiveness analyses showed that incremental cost of abstinence achieved by one smoker with total cost reimbursement comparing with no reimbursement is 1247 USD. Those results were confirmed in other studies [49,50].

In Great Britain the reimbursement of bupropion and NRT costs for smokers willing to cease, together with counseling was introduced in two stages; initially for two weeks (NRT) and 3–4 weeks (bupropion) and, if during the follow-up visit the patient maintains abstinence, the cost reimbursement is prolonged for the following treatment period. If the smoking cessation attempt with those pharmacological substances fails, next prescription can not be made during the next 6 months. The cost reimbursement of pharmacological substances supporting smoking cessation was introduced in New Zealand. The cost reimbursement of pharmacological methods used for treating tobacco dependence should also be considered by Polish health care providers.

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APPENDIX

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Bupropion

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