REVIEW

CURRENT KNOWLEDGE ON BUPROPION AND VARENICLINE CLINICAL EFFICACY IN NICOTINE DEPENDENCE

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Abstract

The purpose of this paper was to investigate the efficacy of bupropion and varenicline for treating nicotine dependence as reported in the published studies. We analysed 435 journal articles identified in Pubmed data base with "nicotine, dependence, bupropion / varencline" included in abstract. The "human" filter was applied. 20 efficacy studies were selected and included for evaluation in this review. The results of these studies support the efficacy of both bupropion and varenicline, with varenicline showing higher abstinence rates. However in real life settings high levels of efficacy are lacking for all current available treatments. In addition, treatment related side effects highly influence the patient compliance.

Rezumat

Scopul acestei lucrări a fost investigarea eficacităţii bupropionei şi a vareniclinei în tratamentul dependenţei la nicotină raportată în studiile publicate în literatură. Au fost identificate şi analizate în baza de date Pubmed 435 de articole care conţineau în rezumat cuvintele cheie "nicotină, dependenţă, bupropiona/vareniclina". Ulterior a fost aplicat filtrul de căutare "subiecţi umani". După aplicarea acestui filtru au fost selectate şi incluse în analiză 20 de studii de eficacitate efectuate pe subiecţi umani. Rezultatele studiilor analizate susţin eficacitatea atât a bupropionei, cât şi a vareniclinei în tratamentul dependenţei la nicotină, vareniclina asociindu-se însă cu o rată mai mare de abstinenţă. Cu toate acestea, în practica actuală curentă eficacitatea tuturor medicamentelor utilizate în tratamentul adicţiei la nicotină este destul de redusă. În plus, efectele adverse ale acestor medicamente influenţează destul de mult complianţa pacienţilor la tratament.

Keywords: nicotine, nicotine dependence, bupropion, varenicline, efficacy

Introduction

Nicotine is a nicotine receptor agonist found in tobacco products that also occurs naturally as autonomous substance. It has pronounced central nervous system (CNS) and cardiovascular effects. Consumption of tobacco products causes nicotine addiction which leads to 94 million smoking-related deaths every year and is the largest cause of preventable mortality in the world. Even though this is a well-known health issue, recognized by smokers as well, smoking continues to be a problem and its prevention is difficult. This is because nicotine from tobacco induces pleasure and CNS stimulation, it reduces the level of stress and anxiety and at the same time it improves concentration, reaction time and also performance in some tasks. On the other side, smoking cessation causes craving and withdrawal symptoms that include a strong urge to smoke, irritability, dysphoria, anxiety, anger, insomnia, depressed mood, concentration difficulties, agitation, increased appetite and also weight gain. In other words, the quality of life is affected dramatically. Thus, nicotine addiction can be considered as a combination of positive reinforcements, like functionality or mood enhancement, and at the same time avoidance of the negative consequences of smoking cessation. A successful smoking cessation therapy should be based on a correct understanding of nicotine pharmacodynamic and pharmacokinetic properties and also the mechanism of nicotine addiction. Nicotine dependence is a major health problem that is associated with high morbidity and premature death. Pharmacotherapy for tobacco dependence is one of the most cost-effective preventive health interventions [11].

Nicotine binds to its specific receptors, facilitating neurotransmitter release that mediates the complex actions of nicotine in tobacco users. Dependence to nicotine begins with nicotine binding to nicotinic acetylcholine receptors (nAChRs) in the central nervous system. Nicotine has 2 optical isomers: S(-) nicotine and R(+)nicotine. Nicotine in tobacco is mostly presented as S(-)-nicotine, R(+)-nicotine, ranging only from ~0.1% to ~1.2% of the total nicotine [1]. The content of nicotnine in ciggares was determined to be, on an average, 15.35 mg/g of tobacco [24]. A big amount of the nicotine absorbed from cigarettes is metabolized by 5'-hydroxylation pathway [8, 19]. S(-)-nicotine is the most pharmacologically active form of nicotine and

it binds stereoselectively to nicotinic cholinergic receptors (nAChRs). (R)-nicotine is a weak agonist of nAChRs. Low doses of S(-)-nicotine have a stimulant action, while high doses have a depressant effect. Administration of S(-)-nicotine affects neurohormonal pathways releasing various neuroregulators (dopamine, acetylcholine, serotonin, noradrenaline, beta-endorphin, growth hormone, vasopressin, ACTH and cortisol). All of these neuromodulators may be involved in the reported behavioural and subjective effects of smoking. Nicotinic acetylcholine receptors (nAChRs) are pentameric cation permeable ligand-gated ion channels that are activated by acetylcholine (ACh) and also by nicotine. At the moment there are 12 neuronal nAChR subunits identified (α2 to α10 and β2 to β 4). The combination of these subunits forms heteromeric channels with the exception of the subset of α7 to α10 which may form homomeric channels.

The electrophysiological properties and agonist-binding affinities of each channel depend on its subunit composition. One of the most important addiction mechanism described for nicotine is the activation of a reward pathway (the circuitry that mediates the feelings of pleasure in the brain).

Dopamine is known to be involved in mediating the desire to consume drugs and nicotine was shown to increase the dopamine levels in the reward circuits. The same mechanism was described in the case of other drugs of abuse.

The pharmacokinetic properties of nicotine are also increasing the addictive potential due to the rapid absorption and distribution in the brain with peak nicotine levels reached within seconds. Even if the acute effects (feelings of reward) are installed rapidly, they however dissipate quickly and thus the smokers feel the urge to continue smoking to maintain the pleasurable effects and to prevent withdrawal symptoms.

Nicotine dependence was found to be highly heritable. Results from genetic studies suggested roles for nicotinic receptor subtypes and also genes involved in neuroplasticity and learning, in development of dependence. It is known that nicotine is primarily metabolized by CYP2A6 and the variability in the rate of metabolism contributes to vulnerability to tobacco dependence, smoking cessation treatment response, and also to lung cancer risk. Nicotine dependence is more frequent in patients with mental illness and substance abuse disorders, this category representing a high proportion of the current smokers [3].

The release of dopamine, gamma aminobutyric acid and glutamate has an important role in the development of nicotine dependence.

Currently first-line smoking cessation therapies include nicotine replacement therapy (NRT) (nicotine patch, sublingual tablet, lozenge, gum, inhaler and nasal spray), bupropion (which is an antidepressant) and varenicline (a nicotinic partial agonist).

Bupropion is a special antidepressant, difficult to be classified within other classes of antidepressants. Bupropion inhibits noradrenaline, dopamine and serotonin transporters, and VMAT2 (vesicular monoamine transporter 2), and in addition it increases the release of noradrenaline and dopamine in the synaptic cleft. Bupropion is providing probably an antidepressant effect of similar intensity as the other antidepressants, but there are cases of major depression which are resistant to other treatments that respond to bupropion. It is considered as an optimal drug to be associated with another antidepressant. Bupropion is also used in the treatment of nicotine dependence in order to aid smoking cessation. Some experimental studies have shown that bupropion competitively inhibits *in vitro* the following nicotine receptors: α3β2, α4β2 or α7. There are hypothesis that bupropion can aid smoking cessation by its antidepressant effect in smokers willing to quit smoking but afraid of doing it.

Varenicline is a partial agonist of α4β2 nicotine receptors in brain, with smaller affinity for α3β4 in autonomic ganglia and very small affinity for α1βγ(ε)δ nicotine receptors (localized in the muscles). Based on these affinities, it is considered that varenicline partially stimulates nicotine receptors reducing the desire to smoke another cigarette. In addition, nicotine delivered by a new puff will find the nicotine receptors blocked so the addition will not be further developed. Peripheral nicotinic effects of varenicline are uncommon (with frequency ≥ 1/1000, <1/ 100). However varenicline can frequently cause side effects like insomnia, abnormal dreams, headache, nausea, increased food appetite. Less frequently panic reactions, dysphoria, bradyphrenia, abnormal thinking, anxiety, mood changes, depression, hallucinations, increased or decreased *libido*, suicidal ideation, psychosis, aggression, somnambulism were reported. Cases of varenicline dependence were also reported. Some efficacy has been demonstrated for also for clonidine and however their side effects are limiting their use [9]. Monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, bromocriptine, opioid receptor antagonists, anxiolytics, nicotinic receptor antagonists (e.g. mecamylamine) and glucose tablets were also tested as treatments of nicotine dependence but with limited efficacy. Other approaches are under investigation such as inhibitors of the hepatic P450 enzymatic system (e.g. methoxsalen), cannabinoid-1 receptor antagonists (e.g. rimonabant), dopamine D3 receptor antagonists and nicotine vaccines. Nicotine vaccines interact

with nicotine in the blood rather than with a receptor in the brain and thus they are considered to lack side effects due to central interaction. Usually the effect of antidrug vaccines is irreversible and they provide long term protection [9].

From a safety point of view, all therapies are commonly associated with a number of adverse effects. Serious adverse effects are rare with nicotine replacement therapy while both bupropion and varenicline were reported to lead to unexplained serious adverse events, including depression, behaviour change, suicidal behaviour, and self-injurious thoughts [11].

Overall, the current treatments for nicotine dependence are effective but still associated with low long-term abstinence rates [11]. In addition, there are safety concerns associated with the use of currently available medication. Thus new treatments continue to be developed.

The purpose of this paper was to investigate the literature data regarding the efficacy of bupropion and varenicline in nicotine dependence therapeutic approach.

Materials and Methods

2 separate literature searches were performed in Pubmed data base, one for bupropion and one for varenicline. Key words for bupropion included: nicotine, dependence, bupropion. For varenicline, the key words included: nicotine, dependence, varenicline. No time limit was applied. The articles were further scrutinized and only efficacy studies with clear efficacy end points (e.g. abstinence rate) were selected. The following studies were excluded: systematic reviews and meta-analysis (in order to eliminate the possibility of duplication of data), studies addressing alcohol dependence or cocaine dependence (as these may influence the efficacy in nicotine dependence), studies assessing efficacy of varenicline and bupropion as part of a treatment combination only (only monotherapy administration was considered), studies in special population (adolescents, pregnant women, smokers with comorbid diseases like schizophrenia or any other psychiatric disorder, chronic obstructive pulmonary disease, cardio-vascular diseases, HIV).

Overall efficacy of bupropion and varenicline were evaluated mainly by means of point prevalence rate and continuous abstinence rate reported in the published studies.

Results and Discussion

In total, 435 journal articles, in humans, were retrieved from Pubmed following the 2 literature searches. 254 articles that included the selected terms in the abstracts were retrieved for bupropion and 181 for varenicline. Out of the 435 articles retrieved, 20 studies were selected (Table I) as follows: 5 noncomparison studies [4, 7, 14, 21, 22], 2 *placebo* controlled studies [2, 8], and 3 comparative studies bupropion versus NRT [6, 23, 25] were selected for addressing the efficacy of bupropion. For varenicline, 2 noncomparison studies [5, 20], 2 placebo-controlled studies [13, 16], and 2 comparative studies varenicline *versus* nicotine replacement therapy (NRT) [12, 15] were selected. In addition, 2 studies comparing varenicline, bupropion and placebo [10, 18] and 2 comparative studies varenicline, bupropion and NRT [17, 26] were selected for addressing the comparative efficacy of bupropion *versus* varenicline.

Table I

Selected efficacy studies on bupropion and varenicline included in the analysis

Nr	Author, year	Study type	Medication	Subjects number
1	Johnstone et al., 2004	noncomparative	Bupropion	239
2	Bergmann et al., 2004	noncomparative	Bupropion	321
3	Roth et al., 2001	noncomparative	Bupropion	71
4	Porebska et al., 2003	noncomparative	Bupropion	54
5	Chatkin et al., 2006	noncomparative	Bupropion	253
6	Aubin et al., 2004	Placebo controlled	Bupropion, Placebo	509
7	Dale et al., 2002	Placebo controlled	Bupropion, Placebo	68
8	Uyar et al., 2007	comparative study	Bupropion, NRT	131
9	Smith et al., 2009	comparative study	Bupropion, NRT	1346
10	Chatkin et al., 2004	comparative study	Bupropion, NRT	381
11	Boudrez et al., 2011	noncomparative	Varenicline	551
12	Onizawa et al., 2010	noncomparative	Varenicline	148
13	Hughes et al., 2011	placebo controlled	Varenicline, Placebo	218
14	Nakamura et al., 2007	placebo controlled	Varenicline, Placebo	618
15	Hsueh et al., 2014	comparative study	Varenicline, NRT	587
16	Kralikova et al., 2013	comparative study	Varenicline, NRT	855
17	Nides et al., 2008	comparative study	Bupropion, Varenicline, Placebo	2052
18	Gonzales et al., 2006	comparative study	Bupropion, Varenicline, Placebo	1025
19	Yilmazel et al., 2014	comparative study	Bupropion, Varenicline, NRT	422
20	Mainar et al., 2011	comparative study	Bupropion, Varenicline, NRT	957

The 20 studies were published in the period 2001 – 2014. There are various differences between the selected studies (including design, study population, dosage administration), but these are not falling under the scope of this paper and will not be addressed here. The overall efficacy of bupropion and varenicline in the selected studies was evaluated by means of point prevalence rate and continuous abstinence rate (CAR). The time points for measuring the point prevalence rates were slightly different from study to study, but this is not affecting the overall conclusion on efficacy.

Bupropion was found to be effective in nicotine dependence providing satisfactory quitting rates at 6 months time point both in non-comparative studies and in *placebo* controlled studies. In comparative studies of bupropion *versus* various NRT, bupropion showed similar efficacy, with higher efficacy only in combination therapies.

In non-comparative studies, the 6 months abstinence rate were as follows: 30% in the study of Johnstone et al (2004); 30.5% in the study of Bergmann et al (2004); 25.4% reported by Roth et al (2001); 45.2% in the study of Porebska et al (2003); and 20.8% in men and 22.7% in women in the study of Chatkin et al (2006) [4, 7, 14, 21, 22].

In *placebo* controlled studies, 6 months point prevalence of abstinence rate were 33.1% with bupropion and 16% with placebo in the study of Aubin et al. (2004) and 29% in both groups in the study of Dale et al (2002). In the last study, subjects on bupropion reported significantly less ($p < \text{or} = 0.034$) nicotine withdrawal than placebo after 7 weeks of medication [2, 8].

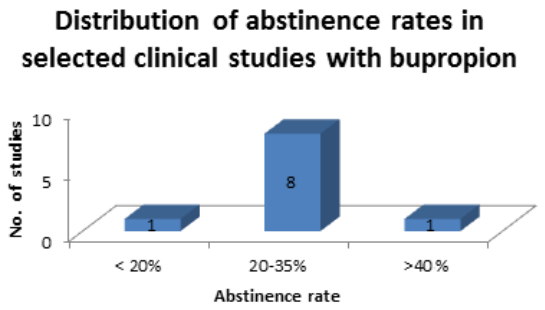

Figure 1.
Abstinence rates distribution in selected bupropion studies
The columns represent the number of studies for each abstinence rate category.

In comparative studies of bupropion *versus* NRT, the success rate was 26% for both, bupropion and NRT and 16% in the control group after 24 weeks as reported by Uyar et al (2007). In the study of Smith et al (2009), 6 months abstinence rates were 16.8% for bupropion SR, 19.9% for lozenge, 17.7% for patch, 26.9% for patch + lozenge, 29.9% for bupropion SR + lozenge. The abstinences rates at 12 months reported by Chatkin et al (2004) were 14.5% for counselling only, 25.4% for counselling + NRT, 22.8% for counselling + bupropion and 38.5% counselling + bupropion + NRT ($P < 0.001$). The distribution of the abstinence rates reported for bupropion in selected studies is presented in Figure 1 [6, 23, 25].

Varenicline was proved to be an effective smoking cessation aid in both comparative and non-comparative studies. In non-comparative studies, the abstinence rate at 12 weeks was 64.6% in the study of Boudrez et al (2011) and 84.6% in Onizawa et al (2010) study. In *placebo* controlled studies, the abstinence rates were 73% for varenciline and 41% for *placebo* at one site in the study of Hughes et al (2011) and 45% *vs* 51% at the second site. In the study of Nakamura et al (2007) the continous abstinence rate for weeks 9–12 was significantly higher for all doses of varenicline compared with *placebo* (39.5%). This study also evaluated the dose response and it showed that varenicline was associated with dose-dependent improvement in smoking abstinence rates during the last 4 weeks of treatment and in the longer term over 40 weeks of nontreatment follow-up. The dose associated with the highest efficacy was varenicline 1 mg twice daily. In the comparative studies of varenicline *versus* NRT, varenicline was shown to be superior. The study of Hsueh et al (2014) showed a significant advantage for varenicline over NRT. In the study of Kralikova et al (2013) the abstinence rates at 52 weeks were 42.85 with varenicline and 31.0% with NRT. The distribution of the abstinence rates reported for varenicline in selected studies is presented in Figure 2 [5, 12, 13, 15, 16].

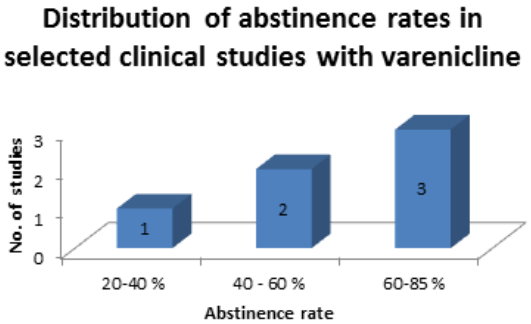

Figure 2.
Abstinence rates distribution in selected varenicline studies
The columns represent the number of studies for each abstinence rate category.

In comparative efficacy studies, varenicline was shown to be superior to bupropion. In the study of Nides et al (2008), continuous abstinence rates

(weeks 9-12) were 44.0 % for varenicline, 29.7 % for bupropion ($p < 0.0001$) and 17.7 % for *placebo* ($p < 0.0001$). The distribution of the abstinence rates reported for bupropion, varenicline and *placebo* in this study is presented in Figure 3 [18].

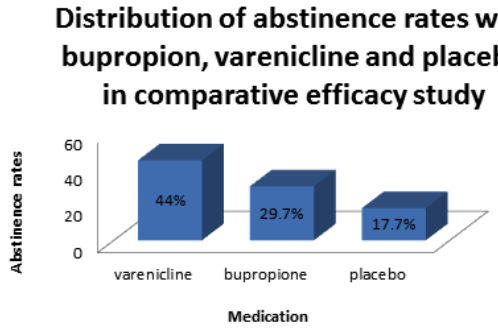

Figure 3.
Abstinence rates distribution reported for bupropion, varenciline and placebo in Nides et al (2008) study. The columns represent the abstinence rates of bupropion, varenciline and placebo as reported in this study.

The same results were reported in the study of Gonzales et al (2006) where the 4-week continuous abstinence rates (for weeks 9 to 12) were 44.0% for varenicline, 17.7% for placebo and 29.5% for bupropion [10]. The mean efficacy for bupropion *versus placebo* and varenicline versus *placebo* were calculated as arithmetic mean abstinence rate using the results from the selected placebo controlled studies. The mean efficacy for bupropion was 30.32% while for placebo was 20.1%. The mean efficacy for varenicline was 52.90% and for placebo was 33.38%. Even if there was a small difference in the mean efficacy between bupropion or varenicline as compared with placebo, these therapeutics approach are providing an overall satisfactory efficacy level. The mean efficacy of bupropion and varenicline *versus placebo* reported in the selected *placebo* controlled studies are presented in Figure 4.

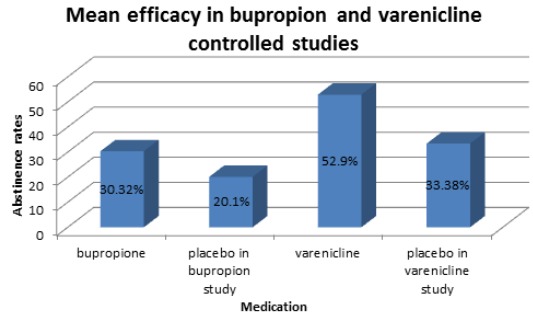

Figure 4.
Mean efficacy of bupropion and varenciline in placebo controlled studies. The columns represent the mean abstinence rates of bupropion *versus placebo* and varenicline *versus placebo* reported in these studies.

2 studies compared NRT with bupropion and varenicline and the results were conflicting. In the study of Yilmazel et al (2014) the smoking cessation rates were 32.5% for varenicline, 23% for bupropion and 52.8%, for nicotine replacement therapy, and were statistically significant ($p > 0.001$), while in the study of Mainar et al (2011) the abstinence rates after 6 months were: 61.2% for varenicline, 56.9% for bupropion, and 52.3% for NRT. After 12 months, the rates of continuous abstinence were 57.4% for varenicline, 52.9% for bupropion and 47.1% for NRT [17, 26].

Quitting smoking abruptly after prolonged, daily consumption induces a withdrawal syndrome consisting of at least four of the following symptoms: dysphoria or depressive mood, difficulty concentrating, impatience, insomnia, irritability, agitation, frustration, anxiety, anger, increased appetite and weight gain and slowed cardiac rhythm. A recognized clinical symptom of the withdrawal syndrome is craving for nicotine.

These symptoms start within hours after the last cigarette. Within the first few days of smoking cessation, the symptoms are strongest felt and most of the times they subside after a few weeks although they can persist for months in rare cases.

Review of literature data showed that both bupropion and varenicline are effective treatments of nicotine dependence providing satisfactory quitting rates in non-comparative studies and in placebo controlled studies.

In comparative efficacy studies, varenicline was shown to be superior to bupropion.

When compared to various NRT, bupropion showed similar efficacy while varenicline was shown to be superior to NRT.

Conflicting results were found when efficacy of NRT, bupropion and varenicline were compared. One study supported superiority of NRT while the second study reported varenicline to be superior.

The current treatment of nicotine dependence includes nicotine replacement therapies, bupropion and varenicline. Other treatments were considered and studied in various clinical trials but their use is limited due to decreased efficacy or safety concerns. The treatments with bupropion, varenicline and NRT seem all to be effective in nicotine dependence, varenicline showing higher abstinence rates. But current approaches were reported to lack high levels of efficacy in real life settings. In addition, treatment related side effects including weight gain affect the patient compliance. Serious side effects have been reported with varenicline and bupropion and these include suicidal thoughts, suicide and depression. In addition, bupropion is associated with an increased risk of seizures because it lowers the seizure threshold [9, 11].

New medications and vaccines promising to have significant clinical advantages are now in the advanced stage of development. These include nicotine vaccines and monoamine type B inhibitors. As failure rates are high and relapse is common, these new therapies would offer more therapeutic options for smoking cessation and solutions to the problem of relapse.

Conclusions

Current literature data suggest that both bupropion and varenicline are effective in nicotine dependence, with varenicline showing higher efficacy.

However, in real life settings all of the current available treatments were reported to lack high levels of efficacy.

In addition, treatment related side effects influence the patient compliance.

New treatment options are awaited to overcome the limited efficacy and relapse issue.

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