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NEW APPROACH FOR NICOTINE DEPENDENCE TREATMENT WITH CYTISINE (TABEX)

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ABSTRACT

Introduction: The aim of this paper is to present new approach for nicotine dependence treatment with Cytisine (Tabex) and to compare it to the dosage regimen, prescribed by the manufacturer.
Material and Methods: 209 patients - smokers intended to quit smoking are divided randomly into two groups. Smokers in the first group are treated with Tabex according to the dosage scheme prescribed by the manufacturer. Patients in the second group are treated according to a new scheme: they stopped smoking from the beginning of the treatment and took 1 tablet of Tabex three times daily. Their treatment with Tabex continued at a dose of one tablet twice a day after the tenth day till 30th day; after 30th day – a maintenance dose of 1 tablet daily for up to 3 months. Both groups of patients were followed-up for one year.
Results and Discussion: The analysis shows that the new approach gives us better results in the tenth day, more sustainable results (after first year).
The observed incidence of adverse events was lower compared to patients treated with dose offered to us by the manufacturer. Despite the lower dose of cytisine, the new scheme is more effective as a nicotine replacement therapy.

INTRODUCTION

Smoking epidemic is one of the greatest threats to public health, which affect billions of people worldwide. (Shafey *et al.,* 2003) Smoking remains to be a major cause for preventable mortality and morbidity in the developed countries. (Chandler *et al.,* Rennard, 2010) WHO has classified nicotine dependence as a disease with code F17 (Mental and behavioural disorders due to use of tobacco) in the Tenth Revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10), which calls for a careful study and thorough knowledge of the mechanism of addiction, and administration of adequate treatment consistent with individual needs of every patient - smoker. Psychosocial skills for work with patients with nicotine dependence are also required. It is also important to pay attention to the work with smokers who have tried and failed quitting and to highly nicotine-dependent smokers who present a high risk for relapse. Therapeutic possibilities should be conformed to the degree of dependence as well. (Chapman et MacKenzie, 2013). There are studies in recent years, which show approaches in the treatment of nicotine dependence that are different from traditional approaches. (Zwar *et al.,* 2012). It has been sown in some studies that nicotine replacement therapy (NRT) can be used concurrently with cigarette smoking so as to gradually reduce cigarette consumption as a prelude to complete quitting (Rennard *et al.,* 2006). Another study shows that the duration of the treatment with nicotine replacement product can be more than 8-12 weeks, as long as necessary for the smoker to quit cigarettes. (Medioni *et al.,*

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2005). Studies have demonstrated that the use of high doses of nicotine products, a combination of more than one medicine form, especially in highly dependent smokers, is significantly more effective (Stead *et al.,* 2012). Four types of products indicated for smoking cessation are offered on the Bulgarian market – nicotine gums, nicotine patches, Tabex and Champix. From them Tabex has the longest history as an agent for nicotine dependence treatment. Several studies pointed the efficacy of this product in the treatment of nicotine dependence, but also it is associated with a high frequency of self-reported adverse events (Etter 2006, Walker 2014, Zatonski 2006, West *et al.,* 2011). Tabex contain cytisine, which is an alkaloid that is a natural extract from Cytisus Laburnum seeds. It is a partial agonist with high affinity to alpha4beta2 subtype of acetylcholine receptors (Tutka *et al.,* Zatonski, 2006, Etter *et al.,* 2008). This receptor subtype is involved in the development and maintenance of nicotine dependence. (Gotti, 2010) Cytisine blocks receptors from their binding to nicotine, reduces nicotine dependence and stimulates dopamine release. Walker *et al*. (2014) summarize that Cytisine is effective for quitting smoking, and can be used as first-line treatment of nicotine dependence. The *aim* of this paper is to present new, more optimal approach for nicotine dependence treatment with Tabex and to compare it to the dosage regimen, prescribed by the manufacturer.

MATERIALS AND METHODS

Study population contains 209 smokers, who have attended free campaigns for lung tests, which have been done in Specialized Hospital for Pulmonary Diseases "St. Sofia" (SHPD "St. Sofia") between 1.01.2004 and 31.12.2010. The observed smokers are randomly split into two groups and are monitored during smoking cessation period of time. Smokers in the *first group* take Tabex according to the standard scheme proposed by the manufacturer include administration of Tabex parallel with smoking (days 1-3: 1 tablet, 6 times a day, every 2 hours). During days 1-3 of the treatment gradual reduction of cigarettes smoked is recommended. If the result appears to be unsatisfactory, treatment should to be discontinued and may be repeated in 2-3 months, as manufacturer prescribed. If the result is satisfying (significant reduction of the number of cigarettes smoked per day), treatment after the third day should continue according to the following scheme: days 4-12: 1 tablet every 2.5 hours (5 tablets daily), days 13-16: 1 tablet every 3 hours (4 tablets daily), days 17-20: 1 tablet every 5 hours (3 tablets daily), days 21-25: 1-2 tablets daily. Final smoking cessation should be achieved on 5^{th} day after treatment initiation.

The patients in the *second group* were treated according to a new approach: they stop smoking from the beginning of the treatment and take 1 tablet of Tabex in the morning (this tablet is prescribed to be sucked out), 1 tablet at noon and 1 tablet at the evening. The rest 3 tablets (maximum daily dose of 6 tablets, according to the manufacturer prescription) were administered only if necessary (strong desire to smoke and/or expressed nervous strain). Treatment with Tabex after the 10^{th} to 30^{th} day continued at a dose of one tablet twice a day, and after 30^{th} day – a maintenance dose of 1 tablet daily for up to 3 months. Data for patients' smoking status for both groups were collected at 10th day and at the end of the first year after treatment initiation by phone call or personally in the consulting unit for smoking cessation at SHPD "St. Sofia". Adverse drug reactions (ADR) were collected at day 10. Tenth day is chosen because it's the time point when the dosage of Tabex is changed for the second group. Patients' age and gender are collected as well as the degree of their nicotine dependence using Fagerstrom test (low dependence: score of 0-2; moderate: score of 3-5 and high dependence: score of 6 and over), (Heatherton *et al*., 1991). Descriptive statistics and Pearson chi square test (Fisher's Exact test when applicable) are applied with a level of significance $P<0.05$. The study met the ethical principles of the Helsinki Declaration, and was carried out after approval by the Specialized Hospital for Pulmonary Diseases "St. Sofia" ethical committee. A written informed consent was obtained from all patients.

RESULTS

Patient description

The patients included in the sample are almost equally distributed according to their gender: 52.6% (n=110) patients are males and 47.4% (n=99) patients – females (Table 1). About half of the smokers (48.3%) have high smoking dependence, more than one third (40.7%) are moderately dependent, and every tenth patient (11%) has low dependence. Adverse drug reactions (ADR) are experienced by almost half of the patients (41.6%) and the most common of them are related to cardiovascular system (CVS), gastrointestinal tract (GIT), vertigo and nervous strain. Almost 2/3 of the smokers (60.8%) continue their treatment after the 10^{th} day, ever if they have stopped smoking. One year after the treatment only 34.9% remain ex-smokers. When analyzing patients by the variables describing smoking status at 10^{th} day and a year after treatment initiation, it can be noticed that the biggest proportion is represented by the persons who neither stop smoking up to 10^{th} day nor a year later (38.8%). A single person who smoked at day 10, at 12^{th} month was reported as an ex-smoker. Every 4^{th} smoker (26.3%) didn't smoke at 10^{th} day, but a year later is still smoker. One third of the patients (34.4%) quit smoking up to 10^{th} day and remains ex-smokers year later.

Reasons for treatment failure

As shown in the Tables 1-2, no gender differences are found in the proportion of failed quitters neither at 10^{th} day, nor a year later. The degree of nicotine dependency is not a cause for 10^{th} day failure. It's controversial if it forms the patients' behavior a year after treatment initiation, bigger is the proportion of those with high dependence who were not able to quit, but not reach the significance level ($P>0.05$) Adverse drug reactions are very likely to be a good reason for treatment failure: ADR, related to CVS, GIT, vertigo, nervous strain and any of the above are related to more frequent failure at 10^{th} day and a year later ($P<0.01$). The ADR could explain most of the treatment failure cases at 10^{th} day and a year later. Some of the patients who were not able to quit at 10^{th} day reported other reasons for their failure, being in parties where other people smoke and provoke them, long travel with smoking companions etc. which is predominantly lack of motivation.

Comparison between the treatments schemes (treatment groups). The results of the analysis related to the treatments schemes are presented in the table 3. The distribution of patients according to their gender and degree of smoking dependence is similar in both groups – treated by the manufacturer prescription (first group) and according the new approach (second group), $P>0.05$.

Table 1. Distribution of the patients by their smoking status at 10th day (Pearson chi-square and Fisher's Exact test), percentage by rows

Variable (category)	Smoke at 10th day		Don't smoke at 10th day		p (2-sided) Pearson chi-square	p (1-sided) Fisher's exact test
	n	%	n	%		
Sex – male	45	40.9	65	59.1	0.607	0.352
Sex – female	37	37.4	62	62.6		
Nicotine dependence – low	5	21.7	18	78.3	0.153	NA*
Nicotine dependence – moderate	33	38.8	52	61.2		
Nicotine dependence – high	44	43.6	57	56.4		
ADR – cardiovascular system	27	90.0	3	10.0	<0.001	<0.001
ADR – gastrointestinal tract	26	92.9	2	7.1	<0.001	<0.001
ADR – nervous strain	12	85.7	2	14.3	<0.001	<0.001
ADR – vertigo	15	93.8	1	6.3	<0.001	<0.001
ADR – no	19	13.8	119	86.2	<0.001	<0.001
ADR –any	63	88.7	8	11.3		

* NA – not applicable

Table 2. Distribution of the patients by their smoking status a year after treatment initiation (Pearson chi-square and Fisher's Exact test), percentage by rows

Variable (category)	Smoke after 1 year		Don't smoke after 1 year		p (2-sided) Pearson chi-square	p (1-sided) Fisher's exact test
	n	%	n	%		
Sex – male	72	65.5	38	34.5	0.903	0.509
Sex – female	64	64.6	35	35.4		
Nicotine dependence – low	10	43.5	13	56.5	0.051	NA*
Nicotine dependence – moderate	55	64.7	30	35.3		
Nicotine dependence – high	71	70.3	30	29.7		
ADR – cardiovascular system	28	93.3	2	6.7	<0.001	<0.001
ADR – gastrointestinal tract	27	96.4	1	3.6	<0.001	<0.001
ADR – nervous strain	14	100.0	0	0.0	0.005	0.002
ADR – vertigo	16	100.0	0	0.0	0.002	0.001
ADR –no	68	49.3	70	50.7	<0.001	<0.001
ADR – any	68	95.8	3	4.2		

* NA – not applicable

Table 3. Distribution of the patients – total and by study groups (Pearson chi-square and Fisher's Exact test), percentage by columns

Variable (category)	Total N=209		First group (manufacturer prescription, Tabex + smoking) n=107 (51.2%)		Second group (new approach, Tabex without smoking) n=102 (48.8%)		p (2-sided) Pearson chi-square	p (1-sided) Fisher's exact test
	n	%	n	%	n	%		
Sex – male	110	52.6	57	53.3	53	52.0	0.850	0.480
Sex – female	99	47.4	50	46.7	49	48.0		
Nicotine dependence – low	23	11.0	13	12.1	10	9.8	0.830	NA*
Nicotine dependence – moderate	85	40.7	42	39.3	43	42.2		
Nicotine dependence – high	101	48.3	52	48.6	49	48.0		
ADR – cardiovascular system	30	14.4	22	20.6	8	7.8	0.009	0.007
ADR – gastrointestinal tract	28	13.4	19	17.8	9	8.8	0.058	0.044
ADR – nervous strain	14	6.7	9	8.4	5	4.9	0.310	0.231
ADR – vertigo	16	7.7	12	11.2	4	3.9	0.047	0.041
ADR – any	71	34.0	48	44.9	23	22.5	0.001	0.001
ADR – no	138	66.0	59	55,1	79	77.5		
Smoke at 10th day	82	39.2	52	48.6	30	29.4	0.005	0.003
Smoke a year later	136	65.1	78	72.9	58	56.9	0.015	0.011
Smoke at 10 day, smoke a year later	81	38.8	51	47.7	30	29.4	0.019	NA*
Smoke 10th day, quit a year later	1	0.5	1	0.9	0	0		
Stop smoking at 10th day, smoke a year later	55	26.3	27	25.2	28	27.5		
Don't smoke at 10th day, don't smoke a year later	72	34.4	28	26.2	44	43.1		

* NA – not applicable

Adverse drug reactions related to the cardiovascular system occurred significantly more frequently among patients in the first group (treated according to the manufacturer prescription), while the proportion of persons without such ADR is greater among those treated with the new approach (second group), P<0.05. Occurring of ADR, related to gastrointestinal tract, is also slightly but not significantly more frequent in the first group of patients (p>0.05). Nevertheless Fisher's Exact test rejects the Null hypothesis if it's 1-sided (the assumption that one of the compared proportions is greater than the other) at acceptable significant level (p<0.05).

ADR, related to nervous strain are also more frequently reported among patients from the first group, but the difference between groups is not significant (P>0.05). Vertigo as ADR also is significantly more frequent in the first group, than in the second and (P<0.05). Reporting of any ADR (related to CVS, GIT, nervous strain and/or vertigo) is also significantly more frequent among the patients from the first group, that the second (P<0.05). Significant difference was observed between the treatment groups in the proportion of the individuals who stopped smoking within a 10-day period from initiation of therapy. The rate of smoking cessation was higher

in the second group (treated with Tabex without smoking cigarettes), compared to the other group of patients (P<0.05). (Fig. 1).

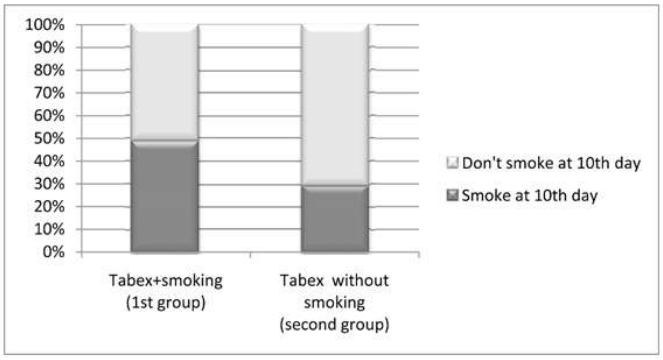

Figure 1. Distribution of the patients according to type of treatment applied, and according to whether they stopped or not smoking till 10th day (proportion; n=209)

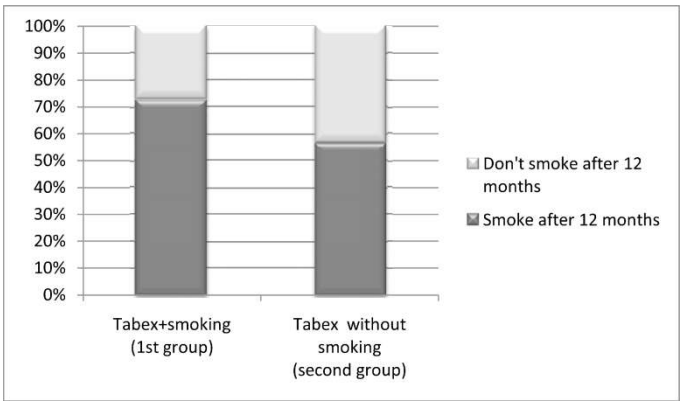

Figure 2. Distribution of the patients according to the type of treatment applied and according to how many of them smoke a year after treatment initiation (proportion; n=209)

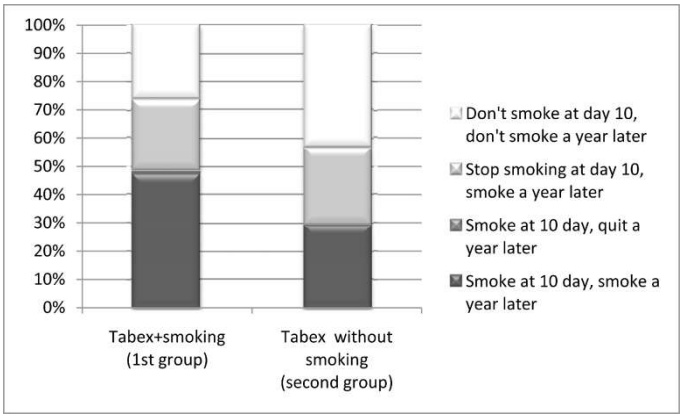

Figure 3. Distribution of the patients according to the type of treatment applied and according to how many of them were smoking at 10th day and one year after treatment initiation (proportion; n=209)

The proportion of those who don't smoke 1 year after treatment initiation is significantly higher among those treated according to the new approach, compared to the others who received treatment prescribed by the manufacturer (P<0.05). (Fig. 2). The proportion of the patients, who have stopped smoking at 10th day and remain ex-smoker 12 months after the treatment initiation (achieved sustainability of the treatment), is significantly higher in the second group (P<0.05). The proportion of those who continue their treatment after 10th day but failed a year later is similar. The share of the patients who were not able to stop neither at 10th day nor a year later is higher among the patients from the first group (P<0.05). (Fig. 3)

DISCUSSION

Adverse drug reactions are the main cause of treatment failure. They could explain almost all cases (about 90%) of the patients who were not able to quit smoking up to 10th day or who smoked a year later. The ADR resulting of Tabex administration, are side effect of Cytisine. The new approach prescribes lower dose of Tabex per day and thus the adverse reactions' frequency among the patients is less. The decrease of the dosage should find the balance between lower ADR reporting and lack of nicotine replacement therapy effect, so the dosage can't be lowered to nil tablets per day in the treatment initiation period of time. The new approach probably has found the limit of decreasing the dosage of Tabex in which the treatment has satisfactory results (almost half of the patients have sustainable results at the end of the first year).

It is important to be highlighted that both methods for treatment of nicotine dependence with Tabex have good results only for those smokers who are firmly motivated to quit smoking cigarettes. Some of the differences in the compared proportions were not reached the significance level. This is probably due to the sample size of this survey which is relatively small. Fisher's Exact test is recommended to be applied in this case, because it's known that Pearson chi-square test underestimates the differences when the sample size is not big. (McDonald, 2014) Larger sample is necessary to prove the results which were not significantly different at 95% degree of certainty.

Conclusions

The analysis of the results for nicotine dependence treatment with nicotine replacement product Tabex show that the new approach in which Tabex is administered by smokers from the day on which they have stopped smoking cigarettes and less quantity of the product is prescribed, have better results at tenth day and more sustainable results (at the end of the first year) mostly because the frequency of the reported adverse drug reactions is less, compared to the approach of administration of Tabex and smoking cigarettes (as prescribed by the manufacturer). Despite of the lower dosage of Cytisine, the new approach is effective as a nicotine dependence treatment. The results give grounds to recommend the new scheme for treatment of nicotine dependence with Tabex to nicotine-dependent patients as being more optimal compared to the one proposed by the manufacturer.

Conflict of interest

The authors declared no conflict of interest.

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