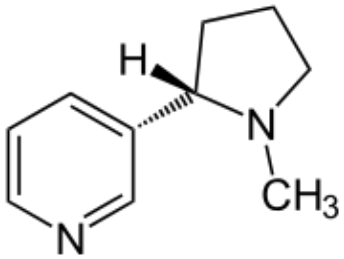
Tabex ® (cytisine and psychiatric adverse reactions) – an update

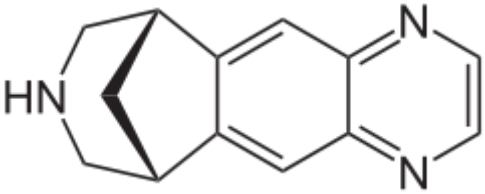
Introduction

Tabex® has been licensed in Eastern Europe as an aid to smoking cessation. The tablets have been produced in Bulgaria since 1964 [1]. In the Netherlands, the drug Tabex® is not registered through the Dutch Medicines Evaluation Board (CBG).The drug is produced in Bulgaria and can be purchased via internet. The active substance in Tabex® is cytisine. The molecular structure of cytisine has similarity to that of varenicline [2]. Varenicline is registered in European Union in 2006 as a drug for smoking cessation therapy, admitted to the European market under the brand name Champix® and in USA under the brand name Chantix® [3]. Varenicline was discovered through the synthesis of a series of compounds inspired by the natural product cytisine, which was previously known to have partial agonist activity at the α4β2 acetylcholine receptor (α4β2 nAChR). Varenicline displaying ~30–60% of the in vivo efficacy of nicotine, and it also effectively blocks the in vivo response to nicotine [4].
In 2017 Lareb informed the Inspectorate for Healthcare and Youth (IGJ) about the 2 cases of psychosis related to the use of Tabex® [5] and in 2019 an update overview was made after receiving a new case of this serious adverse drug reaction after using Tabex® [6].
This overview is an up-date on the received reports.

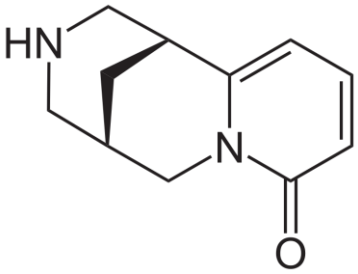
Structural formulas



nicotine



varenicline



cytisine

Reports

Between April 2016 and September 2020 the Netherlands Pharmacovigilance Centre Lareb received seven reports concerning patients who developed psychiatric ADRs after use of Tabex® for smoking cessation. Five reports were submitted by a psychiatrist and two report were reported by a patient.

Table1. Reports of adverse drug reactions associated with Tabex®

No	ID, sex, Age (years) primary source	Drug Dosage Indication	Concomitant medication	Reported ADRs	Latency after start Action taken with the drug Outcome
1	NL-LRB-217162, female, 40-50 Y Physician	Tabex® Smoking cessation therapy		Psychosis	3 Weeks Withdrawn Recovering
2	NL-LRB-231406, female, 50-60 Y Physician	Tabex® 9 milligram / 1 Days Smoking cessation therapy	Pantoprazol	Psychosis	7 Days Withdrawn Recovering
3	NL-LRB-00297145, female, 20-30 Y Physician	Tabex® 1 dosage / 5 h Smoking cessation therapy	Ethinylestradiol/ Levonorgestrel Plantago Ovata	Anxiety aggravated Feeling guilty Absent minded Suicidal ideation Delusions	9 Days Withdrawn Recovering
4	NL-LRB-00342430, female, 50-60 Y Consumer	Tabex® 1 dosage / Smoking cessation therapy	Paroxetine	Psychosis Palpitations Depressed mood	21 Days Withdrawn Recovering
5	NL-LRB-00382209, male, 50-60 Y Physician	Tabex® 3-6 dosage/day Smoking cessation therapy		Panic attacks	Unknown Withdrawn Recovering
6	NL-LRB-00386859, female, 20-30 y Consumer	Tabex® / Smoking cessation therapy		Psychosis Facial paresis Hemiparesis	Not Applicable Unknown
7	NL-LRB-00411175, female, 40-50 Y Physician	Tabex® / Smoking cessation therapy	Natriumlaurylsulfoacet/ Sorbitol Macrogol	Hallucination Vomiting	Unknown Withdrawn Recovered

Case 1- NL-LRB- 217162- A psychiatrist working at a mental health care facility reported about a 40-50 year-old female who developed a psychosis 34 days after start of Tabex® ® for smoking cessation. The product Tabex® was withdrawn. The patient was treated with haloperidol. At the time of reporting, the patient was recovering. Concomitant medication was not reported. The reporter mentions that stress around the time of the event could be an alternative or additional cause for the reaction.

Case 2- NL-LRB- 231406- A Physician working at a mental health care facility reported about a 50-60 year-old women who was hospitalized during three weeks due to a psychosis following administration of Tabex ® for smoking cessation. The dosage used was six times daily 1.5 mg. The reaction occurred one week after start. Tabex ® was withdrawn. The patient was treated with haloperidol 3mg daily and was recovering at the time of the reporting. Concomitant medication was pantoprazole. The reporter mentions that stress around the time of the event could be an alternative or additional cause for the reaction. The patient has a medical history of a post-partum depression and psychosis in 2002.

Case 3- NL-LRB-00297145-A female aged 20-30 years experienced aggravation of anxiety, feeling of guilty, absent minded, suicidal ideation and delusions nine days after start of Tabex® for smoking cessation therapy. She stopped with Tabex® and she was treated with haloperidol. After three weeks

the condition was recovering. Concomitant medication was: ethinylestradiol/levonorgestrel, plantago ovata. She had no medical history. This case was reported by her physician.

Case 4 -NL-LRB-00342430- A female aged 50-60 years reported that she developed a psychosis after three weeks using Tabex® for smoking cessation therapy. She also experienced palpitations and depressed mood. The recommended use implies a tapering down dosage schedule of Tabex ® started with six tablets on the first few days and then in intervals decreasing by one tablet. The symptoms started at the dosage of two tablets per day, this is according the schedule after 21 days of therapy. The patient also used paroxetine, already for 20 years. The symptoms were treated with not specified "calming" and antiarrhythmic medication, prescribed by her general practitioner. The patient was recovering at the time of reporting but she describes this period as something terrible to experience.

Case 5- NL-LRB-00382209-A physician reported a case concerning a 50-60 years old man who purchased Tabex® via web-shop in order to support smoking cessation. After 22 days of use according the recommended schema dosage he experienced panic attacks, sudden crying spells, feeling of going mad and nightmares. He reported no feelings of derealization. There were no clear psycho-social circumstances that could provoke those reactions. He recovered within one months after withdrawal of Tabex® and treatment with oxazepam.

Case 6- NL-LRB-00386859-This report received from a female aged 20-30 years describes psychosis with unilateral numbness /paresis in the face and extremities following administration of Tabex® for smoking cessation therapy. The latency for the occurrence and the outcome of the reported condition is unknown.

Case 7- NL-LRB-00411175-This case reported by a physician concerns a female aged 40-50 years with a history of posttraumatic stress disorder which was adequately treated. After two months of treatment with Tabex® for smoking cessation support she experienced hallucination. The condition started with absence, followed by electric shock sensation and saw everything in black and white. She vomited once. She recovered within minutes. Concomitant medication were laxative enema and macrogol salts.

Product information Tabex®

The patient information leaflets (PILs) that can be found on various websites are confusing. Information about the possible side effects, contraindications and interactions differ between the websites. On some sites for example mental diseases (some forms of schizophrenia) has been notified under the section *Possible side effects* and on an another under the *Contraindications* [2,7, 8,9].

Other sources of information

Literature

The studies on cytisine as a smoking cessation drug, found in the literature revealed no serious adverse events. The most frequently reported adverse reactions were gastrointestinal complaints such as dry mouth, stomachache, nausea and gastric disturbances [1,10,11,12].
The National Institute for Public Health and Environment (RIVM) placed in the 'Evaluation of the Health risks associated with so-called banned herbs' another cytisine containing herb *Genista tinctoria* (dyer's greenweed**)** on the list of the banned herbs. Herbs Laburnum and Cytisus, the source of cytisine in Tabex® ®, are not listed in this report [13].

Mechanism

Cytisine is an alkaloid that occurs naturally in several plant genera, such as Laburnum and Cytisus (Golden Rain, acacia) of the family Fabaceae. Like varenicline, cytisine is a partial agonist of nicotinic acetylcholine receptors. Cytisine binds with high affinity to the $\alpha_4\beta_2$ subtype of the nicotinic acetylcholine receptor [14,15]. This receptor subtype has been implicated in the development and maintenance of nicotine dependence [16] and was the primary target for the drug varenicline, which has proved effective in aiding smoking cessation [17].

Discussion and conclusion

Cytisine is used to help with smoking cessation [1]. It is the active ingredient in de products marketed in the different countries under the different names, such as Tabex® , Nicoferin® , Asmoken®, Desmoxan®, Defumoxan®, Cytisine Aflofarm® . In the Netherlands Asmoken® has been approved by the CBG since March 2018. Tabex® from manufacturer Sopharma has no registration as a medicine in the Netherlands and can be ordered by the Dutch consumers only illegal via internet.

Since Tabex® has no marketing authorization in the Netherlands no official Dutch PIL is available. The Dutch website ikstop.nl, where Tabex® is recommended as one of the possible treatments in smoking cessation, provides an automatic translation (powered by Google) of the PIL from the Sopharma. However, this is incomplete translation and does not mention all the information named in the manufacturer's original English PIL [8]. The information on contraindications, including mental disease is missing here. The consumers who purchase Tabex®, and don't understand English, only read the Dutch patient information on the website. Unfortunately this information is incomplete and therefore may be misleading.

Neuropsychiatric side effects such as psychosis, panic attacks, suicidal ideation, anxiety and hallucinations are not mentions neither in de original information neither on the Dutch website ikstop.nl. The occurring of the psychiatric ADRs with the use of cytisine are to be expected. The molecular structure of cytisine has similarity to that of varenicline (Champix®) and it has similar pharmacological effects. Psychiatric adverse reactions are well known en mentioned in the Summary of the Product Characteristics (SmPC) and in the patient leaflet (PIL) of the Champix®. It also warns against use in patients with a psychiatric history [3].

It is a potential safety risk that Tabex® is illegal available on the Dutch market with the lack of complete Dutch safety information. It is important that consumers are aware of possible psychiatric ADRs related to this product and should be cautioned for use with a medical history of psychiatric diseases. Therefore these product should not be used without consultation of a medical doctor

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This signal has been raised on September 30, 2020. It is possible that in the meantime other information became available.