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Comparison of first-line smoking cessation medications and the theory of new smoking cessation drugs

Xinlei Xie

Beijing New Oriental Foreign Language School at Yangzhou, Yangzhou, China

458998731@qq.com

Abstract. Tobacco dependence is a global public health problem. A large number of people use cigarettes, which causes lung diseases not only in smokers but also in people around them. This article will use both a review and literature analysis to study the mechanisms of tobacco addiction, compare frontline smoking cessation medications, their safety and new theories on smoking cessation. The conclusion is that among the three main first-line smoking cessation drugs - varenicline tartrate, bupropion hydrochloride and Nicotine Replacement Therapy (NRT)-the smoking cessation effect of varenicline tartrate is comparable to that of the combination of NRT. Both of these are superior to bupropion hydrochloride and the single use of nicotine replacement therapy. For both bupropion hydrochloride and varenicline tartrate, both have side effects such as insomnia and dry mouth. And varenicline has abnormal dreams as a side effect, especially. Neither is it recommended for patients with epilepsy, teenagers, or pregnant women to use.

Keywords: smoking-cessation agent, nicotine dependence, varenicline, bupropion

1. Introduction

Tobacco dependence is a global public health problem. According to the World Health Organization global report, over 20% of adults smoke [1]. While smoking brings numerous disadvantages. For example, smoking and secondhand smoke exposure lead to over 30% mortality rate of coronary heart disease [2]. Simple ways of quitting smoking are difficult to achieve the desired effect of quitting. Therefore, the use of smoking cessation drugs as an aid to quitting has become a common way of quitting smoking. This article adopts a combined approach of review and literature analysis to study the mechanism of tobacco addiction, comparing the working mechanisms, success rates of quitting smoking, side effects and contraindications of current smoking cessation drugs. It also points out the limitations and existing controversies. This article can be an option for smoking cessation medications are available for reference and for future research.

2. Mechanism of tobacco addiction

Nicotine components in tobacco can bind to Nicotinic Acetylcholine Receptors (nAChRs) on neurons, especially the α4β2 subtype receptors [3]. These receptors are normally activated by endogenous acetylcholine signals, but nicotine, due to its structural similarity, "mimics" and activates them instead. The activated

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receptors are primarily located on dopamine neurons in the Ventral Tegmental Area (VTA). When nicotine binds to α4β2 nAChRs, it significantly increases the firing frequency and burst firing of dopamine neurons, leading to enhanced dopamine release in the Nucleus Accumbens (NAc) and producing a strong sense of reward, thereby positively reinforcing smoking behavior. This represents the common final pathway shared by all addictive drugs [4].

Long-term smoking leads to adaptive changes in the brain - the number of receptors increases, and synaptic connections are reshaped. Once the nicotine concentration in the body drops (such as when quitting smoking), a large number of "idle" receptors cannot be activated, triggering withdrawal symptoms such as anxiety and irritability. At the same time, the association between smoking and rewards is solidified in the neural circuits, forming an indelible "addiction memory" [2].

3. Comparison of first-line smoking cessation medications

Nowadays, varenicline tartrate, bupropion hydrochloride and nicotine replacement therapy are the three main first-line smoking cessation drugs.

3.1. Comparision of mechanism of these drugs for smoking cessation

3.1.1. Mechanism of varenicline tartrate

Varenicline tartrate targets the core receptor of the nicotine addiction pathway directly as a partial agonist of the α4β2 receptor.

Varenicline is A highly selective partial agonist of the nicotine-type acetylcholine receptor α4β2 subtype. Partial agonist means it can both act as an agonist and antagonist on the receptor, forming a unique bidirectional regulation [5].

As an agonist, Varenicline binds to α4β2 nAChRs, which can stimulate receptor-mediated activity, thereby prompting the release of a small amount of dopamine in the mesolimbic dopamine system. Varenicline has a maximum efficacy on the α4β2 receptor that is approximately 45% of that of nicotine. This about half amount of dopamine release is sufficient to produce a moderate sense of pleasure, alleviating the craving for tobacco and the anxiety, irritability and other withdrawal symptoms experienced by smokers attempting to quit.

As an antagonist, varenicline can block the pleasure derived from smoking. Varenicline has a high affinity for the receptor and can competitively occupy the α4β2 receptor, preventing nicotine from binding to the same receptor. When the user smokes, nicotine cannot effectively activate the receptor, which cannot stimulate the release of dopamine in large quantities as before. The pleasure brought by smoking is significantly weakened, reducing the behavioral reinforcement of reward [6].

3.1.2. Mechanism of bupropion hydrochloride

Bupropion is a non-selective inhibitor of Dopamine Transporter (DAT) and Norepinephrine Transporter (NET). It increases the concentrations of these two neurotransmitters in the synaptic cleft by preventing the presynaptic membrane from reuptaking dopamine and norepinephrine [7].

After stopping smoking, nicotine disappears and dopamine levels drop sharply, triggering withdrawal symptoms such as anxiety and irritability. Bupropion maintains the levels of dopamine and norepinephrine in the brain, mimicking the effects of nicotine on these two neurotransmitters, thereby alleviating withdrawal symptoms and reducing the craving for tobacco.

3.1.3. Mechanism of nicotine replacement therapy

While smoking, nicotine is absorbed from the lungs into the blood, and then quickly reaches the brain in a few seconds. Activating receptors on the nAChRs activates dopamine neurons in the Ventral Tegmental area (VTA)

and promotes the release of dopamine in the nucleus accumbens. After quitting smoking, nicotine suddenly disappears and dopamine levels drop. Smokers will get withdrawal symptoms such as anxiety, irritability, and craving. NRT works by continuously introducing a low dose of nicotine into the body, partially activating the same receptor pathway, thus maintaining dopamine levels at a level that is not too low during the withdrawal period, thereby reducing the severity of withdrawal symptoms. It also provides a similar mechanism to reduce the smoking reward [8].

3.2. Comparison of smoking cessation rate

A study conducted a meta-analysis involving 267 studies with a total of 101,804 participants. The results showed that both NRT and bupropion were more effective in smoking cessation than placebo, and their efficacy was similar. Varenicline was more effective in smoking cessation than bupropion and single-form NRT, but its efficacy was comparable to the combined form of NRT. In terms of safety, neither varenicline nor bupropion significantly increased the risk of severe neurological and cardiovascular adverse events; the risk of epilepsy with bupropion was approximately 1/1500, which was lower than the previously estimated level [9].

3.3. Side effects and contraindications

This section mainly compares varenicline and bupropion.

Varenicline has extremely high selectivity for the α4β2 receptor, and its binding affinity to this receptor subtype is much stronger than that of other nicotinic receptors - more than 500 times that of α3β4, more than 3,500 times that of α7, and more than 20,000 times that of α1βγδ. This high selectivity enables its action to precisely target addiction-related pathways, reducing off-target effects [6].

Both bupropion and varenicline bring side effects, mainly insomnia and dry mouth. Besides, varenicline brings nausea, abnormal dream as well [10].

Regarding the contraindications, bupropion is prohibited for individuals with a history of epilepsy. Both of these drugs are not recommended for patients with mental disorders, teenagers, or pregnant women.

4. The theory of new smoking cessation drugs

The current smoking cessation drugs, such as varenicline, bupropion, and nicotine replacement therapy, are helpful for some smokers to quit smoking, but the long-term relapse rate is still high, and their side effects also limit their clinical application. Therefore, researchers have conducted more studies to find other effective smoking cessation drugs.

One of the studies found that G Protein-coupled Receptor 3 (GPR3) is a new target.

Through experiments on mice, it was discovered that the GPR3 selective agonist can significantly reduce nicotine intake at different dose levels; by knocking out the GPR3 gene fragment in mice, the drug is ineffective and no longer reduces nicotine intake. This proves that the effect depends on the GPR3 target. The GPR3 selective agonist does not interfere with anxiety behaviors and motor abilities; at low doses, it does not affect the reward effect of food, and the effect is selective for nicotine [11, 12].

Meanwhile, other drugs from other fields have also been found to have new effects and can be used as smoking cessation drugs. For example, the Glucagon-Like Peptide-19 (GLP-1) receptor was originally a target for treating diabetes and obesity. And GLP-1 Receptor Agonists (GLP-1RAs) have been studied to also act on the reward circuit (VTA), which can have an auxiliary effect on smoking cessation and to some extent inhibit appetite, preventing weight gain after quitting smoking [13]. Therefore, GLP-1RAs drugs as smoking

cessation drugs have additional advantages for groups that are worried about weight gain after quitting smoking.

5. Conclusion

This article mainly discusses the mechanism of nicotine addiction, the working principles of three first-line smoking cessation drugs, the smoking cessation rate, safety, side effects, and contraindications, and the theory of new smoking cessation drugs. As a result, among varenicline tartrate, bupropion hydrochloride and Nicotine Replacement Therapy (NRT), the smoking cessation effect of varenicline tartrate is comparable to that of the combination of NRT. Both of these are superior to bupropion hydrochloride and the single use of NRT.

Varenicline and bupropion both have side effects such as insomnia and dry mouth. Varenicline additionally has a common side effect of abnormal dreams.

This article has some shortcomings as well. This article did not use methods such as case analysis, data analysis, questionnaire surveys, experiments, modeling, etc. for research. There were no more vivid and graphic presentation forms such as tables and graphs. Future studies can seek more new targets to eliminate or reduce the side effects of existing drugs, as well as discover more other drugs with new efficacy as smoking cessation medications.

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