Review Article

TREATMENT OF NICOTINE DEPENDENCE: AN UPDATE

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ABSTRACT

Nicotine is the most common substance of abuse in India, and the most neglected substance of abuse. Nicotine dependence is a significant public health problem. Effective assessment tools for those with the condition include Fagerstrom's test for nicotine dependence and carbon monoxide concentration of expired air. Nicotine Replacement Therapy (NRT) or bupropion doubles the quit rates, and varenicline triples them. There is no difference in efficacy between the five forms of NRT currently available. NRT in combination with varenicline or bupropion would be of a greater benefit than NRT alone. Data on e-cigarettes are inconclusive as of now. Psychosocial interventions with proven efficacy include setting of a quit date, brief advice, motivational interviewing, and group behavioral programs. A combination of pharmacological and behavioral strategies is most likely to produce the best results. Treatments under development include those based on the principles of pharmacogenetics, agents targeting the cognitive dysfunction that accompanies nicotine withdrawal, and nicotine vaccine.

Keywords: Nicotine dependence, management, bupropion, varenicline

INTRODUCTION

Nicotine has a very high addiction potential and is the most common substance of dependence in India.[1,2] World Health Organization estimates that the global yearly death toll as a result of tobacco use is currently six million (including exposure to second hand smoke), and adds that in India there has been an increase in the prevalence of any form of tobacco use from 13.7% in 2008 to 14.6% in 2010.[3] Tobacco use in Kerala is similar in prevalence to the national average, and the annual deaths due to tobacco use in Kerala are estimated to be around 24,000.[4]

Clinicians often tend to neglect nicotine abuse in their patients, and inadvertently miss out counseling them against it.[5,6] As per a report by the Agency for Healthcare Research and Quality, almost half of all smokers had a routine medical checkup in 2003, but only 63.6% of them were counseled by a physician to stop smoking.[7] All health professionals need to be vigilant

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about nicotine use in their patients — This is especially true for mental health professionals, as nicotine dependence is highly comorbid with other psychiatric disorders.[8,9]

ASSESSMENT

Though time consuming, the importance of a proper assessment of the nature and severity of nicotine dependence can never be underestimated. The Fagerstrom's test for nicotine dependence is a handy tool to assess severity of the addiction and to help choose the mode of treatment.[10] Carbon monoxide concentration of expired air is a measure of smoke intake over preceding hours. It gives immediate feedback to the smoker and is especially useful during follow-ups.

The 5 A's of smoking cessation is a brief, useful guideline for assessment and management:[11]

1. *Ask* every patient on every visit about his or her use status, and systematically identify all users. Record tobacco use status prominently along with vital signs.
2. *Advise* all users strongly to quit. Tailor the advice toward the patients' current medical problems and concerns.
3. *Assess* the patient's willingness to quit. Ask every user if he or she is willing to make a quit attempt. If the answer is no, provide motivational interventions.
4. *Assist* patients in their efforts to quit. Provide nicotine replacement and/or pharmacotherapy. Teach behavioral strategies that will help to stop smoking, deal with withdrawal, and prevent relapse.
5. *Arrange* a follow-up close around the quit date to assure the patient that assistance and counseling are available. Arrange subsequent follow-ups to provide support.

TREATMENT: PHARMACOLOGICAL APPROACHES

Nicotine Replacement Therapy (NRT): Replacement therapies are based on the principle of making available to the patient a safer and more therapeutically manageable form of the drug that directly alleviates the signs and symptoms of withdrawal and craving. NRT is of high benefit in nicotine dependence and is widely used. Many studies that assess the efficacy of other pharmacological agents in nicotine dependence have even used NRT as a comparison arm.[12,13,14,15,16]

Currently, five NRTs are approved by the FDA for nicotine dependence: transdermal patch, gum, nasal spray, inhaler and lozenge. Nicotine gum is a nicotine resin complex in which nicotine is incorporated into an ion exchange resin base, which allows release of nicotine in a proper environment (i.e. saliva in the mouth) with appropriate physical pressure (i.e., chewing). Patients with dentures and temporomandibular joint problems may have difficulty chewing the gum. Nicotine lozenge, which is also available over the counter, delivers 25% greater nicotine than the gum. Nicotine transdermal patch can avoid compliance and chewing problems related to the gum; but unlike other NRTs, it cannot provide immediate relief for uncontrollable urges. The nicotine nasal spray delivers a gel-like droplet of nicotine into the nose from a small vial which allows rapid and efficient absorption. With the inhaler, nicotine is absorbed through the buccal mucosa, in contrast to the absorption through the lungs with cigarette smoking.[17] As per a review, six trials have directly compared the various types of NRT with respect to their efficacy, and none could find any significant difference between them.[18]

Patients should be clearly instructed on the use of the NRT formulation. Faulty use leads to inadequate delivery and treatment failure. Until a few years back, guidelines used to suggest that smokers should begin NRT on their quit date, that only one NRT formulation should be used at a time, that one should not use NRT while smoking, and that NRT use should not be continued beyond three months.[19] However, in the light of new research, a recent commentary on FDA labeling on NRT makes the following valid suggestions:[20]

1. Combination NRT, i.e. the simultaneous use of a long acting form like nicotine patch with a faster acting form like nicotine gum, is efficacious and safe.[21, 22]
2. Use of NRT before the quit date is safe and may increase abstinence rates.[23, 24]
3. An extended use of NRT beyond the usual three month duration is safe and may be an effective relapse prevention intervention for some smokers.[15, 24]

NRT seems to improve the cognitive symptoms related to withdrawal. However, it does not necessarily alter the activities of neural circuits, such as the cingulate cortices, that are associated with craving in nicotinedependence.[25] Hence we would be right in assuming that NRT in combination with anticraving agents would be of a greater benefit than NRT alone.

There is some evidence that e-cigarettes help smokers to quit on a long term and that it has no significant adverse effects. However, more research is needed on it before we can make valid conclusions.[26]

Anticraving agents: Various pharmacological options exist for the management of craving for nicotine.

Bupropion has FDA approval for smoking cessation. It is presumed to reduce cravings associated with nicotine deprivation by affecting noradrenaline and dopamine, the two key components of the nicotine addiction pathway. It is also assumed to have an indirect action on the nicotine receptors, thus reducing the reinforcing effects of nicotine. Compared to placebo, bupropion monotherapy doubles the cessation rates. Combination of bupropion with minimal or moderate counseling has been associated with 1-year quit rates of 23.6 - 33.2% in actual practice settings.[1]

Bupropion treatment is started 1-2 weeks before the set quit date, and the usual starting dose of bupropion SR for smoking cessation is 150 mg per day. The dose is gradually increased to 300 mg per day in seven days and that dose is continued for 7-12 weeks after the quit date.[27] Maintenance therapy may go on for six months. Some of the adverse effects reported include insomnia, gastrointestinal upset, appetite suppression, weight loss, headache and lowering of seizure threshold. It is contraindicated in epilepsy, eating disorders, and pregnancy.[1]

Varenicline is a selective partial agonist at the $\alpha 4\beta 2$ nicotinic acetylcholinergic receptor. When this receptor is stimulated by partial agonists like varenicline, the magnitude of the response is lower than that achieved by pure agonists like nicotine. Hence varenicline helps those with nicotine dependence in two ways:

1. Acting as agonist, it helps maintain moderate levels of dopamine and counteract the withdrawal symptoms.
2. Acting as antagonist, it reduces the satisfaction associated with smoking.

While bupropion or NRT doubles quit rates, varenicline triples them.[28] A recent randomized, blinded, placebo-controlled, multi-centered clinical trial (n=446) found

that varenicline in combination with NRT was more effective than varenicline alone at achieving abstinence at twelve weeks (end of treatment) and at six months follow-up.[29]

The major side effect is nausea which occurs in 30% of patients. Varenicline may also cause psychiatric problems like changes in behavior, hostility, agitation, depressed mood and suicidal thoughts or actions, and these are highlighted in the Patient Medication Guide by the FDA.[30] The mechanism behind these side effects is unclear. Varenicline is usually started one week before the target quit date, up-titrated to 1 mg twice daily, and continued for 12–24 weeks.[31] The high cost of the drug limits its use, especially in developing countries.

TREATMENT: NONPHARMACOLOGICAL APPROACHES

Nonpharmacological approaches also play a vital role in the treatment of nicotine dependence. The importance of devising appropriate behavioral strategies tailored to individual patients can never be underestimated. The US Public Health Service Guideline, for example, recommends a combined behavioral and pharmacological approach.[32]

The setting of a quit date, preferably of personal importance to the patient, within two weeks of the consultation, improves the motivation to quit.[1] It would help further to inform family and friends about the decision to quit, and to remove cigarettes and related cues from the environment.[33] Both the nicotine fading technique, which involves achieving a reduction of more than 50% of initial use by the quit date, and the cold turkey method of giving up all of a sudden on the quit date are found to be useful.[1]

Patients should be informed that even a single puff can induce a full relapse, and be trained to identify high risk situations and willfully deal with them. Alcohol and other possible triggering factors should be best avoided. The clinician should provide a supportive clinical environment, encourage the decision to quit, and schedule regular follow-ups. During successive follow-ups, it is important to congratulate the patient's success if he or she is completely abstinent. If lapses have been there, the circumstances that led to them have to be reviewed and specifically addressed.[33]

Brief advice by general practitioners (GPs) leads to 1 - 3 out of 100 smokers receiving it to give up smoking for at least six months in addition to the number who would have stopped anyway.[34] Around 40% of smokers make some form of attempt to quit in response to brief advice from a GP. Though brief interventions take only 5 to 10 minutes, in certain time-bound settings health professionals find it difficult to spare even that much time to discuss smoking cessation.[34] Psychiatrists should consider training their GP colleagues on the importance and techniques of brief intervention. Motivational interviewing, a directive patient centered style of counseling, developed as a treatment for alcohol abuse, may also be employed in this context.[35]

There is a lack of significant progress in the field of behavioral intervention for smoking cessation. One reason for this is the lack of a shared language to describe the detailed content of smoking cessation interventions. In an attempt to rectify this deficit, the UK Medical Research Council has recently funded the Behavior Change Techniques Taxonomy (BCTT) Project, the aim of which is to develop a reliable method for specifying behavior change techniques, linking them to relevant theory, and detailing the behaviors necessary to implement them.[36]

Group behavioral programs are also effective. Nicotine Anonymous groups are active worldwide. Those attending group behavioral programs are twice as likely to quit as compared to those who receive self-help material without a face-to-face behavioral support.[37] Newer methods like telephone counseling are being evaluated. Quit rates with telephonic counseling are higher than those with less intensive interventions such as self-help materials, brief advice, or pharmacotherapy alone.[38] A mobile phone based text messaging service, as studied by a single blind randomized trial, significantly improved smoking cessation rates.[39] A mobile phone based app for smoking cessation — SF28 (SmokeFree28) — was found beneficial in some smokers.[40] The benefit of supplementing smoking cessation programs with physical exercise is not very robust, as reviewed by Ussher et al.[41] There were a few studies showing this benefit — but as per the review, those studies did not have adequate sample sizes, and more studies are required before making valid conclusions.

Stepped care models of psychosocial intervention, which involves providing a more intensive therapy to non-responders, could be thought of as a useful strategy. However, a study on the method did not suggest a significant utility, apparently due to inadequate sample size.[42]

FUTURE PERSPECTIVES

Newer treatment methods need to be devised based on further research directed at elucidating the neurobiological mechanisms underlying addiction. The psychotherapeutic methods too require further refinement for ease and practicability of use.

Pharmacogenetics: Biomarkers of genetic variability in nicotine metabolism (referred to as the nicotine metabolite ratio) and dopamine genotypes may be useful for guiding treatment selection. Slower metabolizers of nicotine may be appropriate candidates for NRT, whereas faster metabolizers may be better candidates for bupropion. Carriers of the Met/Met allele of the COMT gene, which affects DA release, appear to be more suited for NRT; whereas carriers of the long allele of DRD4 appear to be good candidates for bupropion.[43] However, more research is needed to elicit precise pharmacogenomic associations.

Addressing cognitive dysfunction: Nicotine withdrawal is associated with deficits in neurocognitive functions, including sustained attention, working memory and response inhibition. A better understanding of the mechanisms underlying withdrawal-related cognitive deficits may lead to improvements in the treatment of nicotine dependence, and such cognitive deficits could be a target of upcoming therapies.[44]

Nicotine vaccines: Nicotine vaccines act by reducing the amount of nicotine reaching the brain. Though not licensed for public use now, it could be a useful approach in the future.[45]

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