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Short-term efficacy of nicotine replacement therapy for smoking cessation in adolescents: A randomized controlled trial

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ABSTRACT

The aim of this randomized, double-blind placebo-controlled clinical trial is to test the efficacy and safety of nicotine replacement therapy (NRT) in promoting end-of-treatment abstinence among adolescents and whether this relation is moderated by medication compliance. Participants ($N = 257$, age: 16.7 ± 1.13 years) attended an information meeting followed by a 6- or 9-week treatment. Self-reported smoking cessation, compliance, and side effects were measured by means of online questionnaires. Intent-to-treat analyses showed that independent of compliance, NRT is effective in promoting abstinence rates after 2 weeks (OR = 2.02, 95% CI = 1.11–3.69), but not end-of-treatment abstinence. However, end-of-treatment abstinence rates significantly increased in high-compliant (OR = 1.09, 95% CI = 1.01–1.17) and not in low-compliant participants. No serious adverse events were found. Future research is warranted to disentangle the process involving the decrease in abstinence rates and compliance rates from the third week after the quit date onwards.

1. Introduction

Over 80% of adult smokers begin smoking prior to age 18 (Centers for Disease Control and Prevention, 2009). Although the number of adolescent smokers has declined over recent years, the prevalence of current cigarette use in 2011 in U.S. high school students was still 15.8% (Centers for Disease Control and Prevention, 2012) and 18% in Dutch adolescents (STIVORO, 2012). Until now, The Dutch Tobacco Act holds a ban on selling tobacco products to young people under the age of 16; however, currently the government is planning to amend the law by increasing this to the age of 18. To ensure that adolescents are well-informed and can stand up to the pressure to smoke, The Ministry of Health, Welfare and Sport provides education kits for schools, online programs and interventions. Although the majority (60.9%) of adolescents who ever smoked on a daily basis has tried to quit smoking, only 12.2% were successful (Centers for Disease Control and Prevention, 2009).

An important cause of unsuccessful smoking cessation is the occurrence of nicotine dependence symptoms (Kleinjan, van den Eijnden, & Engels, 2009), such as withdrawal and craving (Bagot, Heishman, & Moolchan, 2007; Van Zundert, Boogerd, Vermulst, & Engels, 2009), which may already be experienced by young adolescent smokers (DiFranza et al., 2002). Nicotine replacement therapy (NRT) aims at reducing relapse as it mainly acts by stimulating nicotinic receptors in the brain responsible for the release of dopamine, leading to a reduction in withdrawal symptoms and craving, thereby achieving (more) sustainable abstinence (Molyneux et al., 2006; Stead, Perera, Bullen, Mant, & Lancaster, 2008). An increase in smoking cessation rates by 50% to 70% is demonstrated in a Cochrane review among adult smokers NRT (e.g. transdermal patches) (Stead et al., 2008).

The Food and Drug Administration approved five NRT treatments for adult smoking cessation (i.e. nicotine gum, nicotine inhaler, nicotine lozenge, nicotine nasal spray, and nicotine patch). Some researchers and clinicians have had reservations about treating adolescents with NRT based on a tendency towards a lighter/less regular pattern of smoking among youngsters in combination with concerns about the neurotoxic effects of nicotine on the adolescent brain (Breland, Colby, Dino, Smith, & Taylor, 2009). Nevertheless, the similarity in nicotine dependence and in the behavior at different stages of the smoking cessation process between adolescents and adults asks for examining whether NRT will also be effective for adolescents (Pallonen, 1998). NRT is currently not recommended for treatment of adolescent smokers because of insufficient evidence (Fiore et al., 2008). Recently, two research articles, a meta-analysis and a review, reported on the effectiveness and tolerability of pharmacological therapies in adolescent smokers. The review (Bailey et al., 2012) consisted of 1 lab-based study, 3 open-label studies and 6 RCTs, regarding effects of nicotine patch, nicotine gum, nicotine nasal spray, bupropion, and varenicline. The meta-analysis (Kim et al., 2011) exclusively focused on the 6 RCTs, and included the same

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pharmacological therapies as those in the review, except for varenicline. The review concluded that there is some evidence for efficacy of nicotine patch and bupropion immediately after the end of treatment, but none of the medications included were efficacious in promoting long-term smoking cessation. By contrast, the authors of the meta-analysis concluded that pharmacological treatment for smoking cessation by adolescent smokers does not result in a significant effect on short-term and mid-term abstinence rates. In addition, both the meta-analysis and the review concluded that side effect profiles of the pharmacological therapies were similar to those reported in adult studies, and that these pharmacological therapies appeared to be safe and well tolerated by adolescents. Several explanations were presented for the non-significant findings, such as the small sample sizes and the low abstinence and compliance rates in adolescent smokers.

Another important shortcoming of the previous empirical studies is that, despite the measurement of compliance rates in studies with RCT designs, compliance was neither included as a covariate, nor as a moderator while examining the effect of NRT on smoking cessation. Compliance is defined as 'patient's behaviors (in terms of taking medication, following diets, or executing life style changes) coincide with healthcare providers' recommendations for health and medical advice' (Sackett, 1976). Two other terms have been used interchangeably with compliance in clinical practice (Jin, Sklar, Oh, & Li, 2008), that is, adherence (with a focus on the patient's freedom to decide whether to adhere to the doctor's recommendations (Inkster, Donnan, MacDonald, Sullivan, & Fahey, 2006)) and concordance (with a focus on the patient as a decision-maker in the process and denoting patients–prescribers agreement and harmony (Vermeire, Hearnshaw, van Royen, & Denekens, 2001)). Despite the slight and subtle differences between these terms we will use the term compliance in the present study. Clearly, the efficacy of NRT on achieving abstinence will strongly depend on medication compliance, because even the most efficacious pharmacological therapies will turn out to be ineffective in case of low compliance (Hack & Chow, 2001). Therefore, it is pivotal to take medication compliance into account when testing the effect of NRT, especially since compliance rates were low in previous studies.

Previous studies used abstinence at end-of-treatment as the shortest follow-up measurement. However, it has been shown that sustained smoking cessation success is associated with smoking status in the recent past in adults (Kenford et al., 1994; Shiffman, Sweeney, Ferguson, Sembower, & Gitchell, 2008). Moreover, abstinence rates are higher in the first weeks of treatment than at end of treatment (e.g., Stapleton & Sutherland, 2011). To examine whether this pattern is also occurring among adolescents, we used two outcome measures of abstinence, that is, abstinence after 2 weeks and end-of-treatment abstinence.

Since the results of previous research on the short-term efficacy of NRT among adolescents were inconsistent, the first aim of the present study is to test the efficacy of NRT on smoking cessation after 2 weeks and at end of treatment among youngsters. We thereby extended previous studies by the use of a relatively large sample of adolescents and by substantial efforts to prevent high drop-out and low compliance rates. As previous studies showed low compliance rates while these were not included in the efficacy analyses, the second aim of the study was to examine the efficacy of NRT on smoking cessation after 2 weeks and at end of treatment while taking into account the potential moderating effect of therapy compliance. Because nicotine patches were suggested to be more efficacious than other nicotine replacement products that have been tested among adolescent smokers (Bailey et al., 2012; Moolchan et al., 2005), the present study focused on the efficacy of nicotine patches compared to placebo patches. We hypothesized that higher quit rates would be achieved in the nicotine patch condition than in the placebo patch condition, but only in case of high compliance in patch use. The third aim of the study was to examine whether the nicotine patches cause any serious adverse events. Based on previous research (Bailey et al., 2012; Kim et al., 2011) we expected no serious detrimental side effects resulting from the nicotine patch use.

2. Materials and methods

2.1. Study design

For this randomized, double-blind placebo-controlled clinical trial, adolescents were randomized according to a computer-generated randomization list by the pharmacy of the University Medical Centre to either (1) active study medication (nicotine patch) or (2) an identically appearing placebo (placebo patch). Novartis provided the study medication (Nicotinell and placebo, 21 mg, 14 mg, and 7 mg, identical in appearance), but did not participate in the study design, study performance, or data analysis. Participants were recruited from September till November 2010. This study is part of a long-term follow-up study registered at TrialRegister.nl (NTR3031), which was approved in September 2010 by the Medical Ethical Committee of the Utrecht Medical Centre.

2.2. Procedure

After a search on the Internet, 66 public secondary schools in the central region of The Netherlands were randomly selected and invited to participate in the study; 33 schools granted permission to participate (Fig. 1). For the recruitment of participants, research assistants visited the schools during lunch breaks, handed out flyers, and left posters. In addition, posters and flyers were distributed at higher vocational education, and banners were placed on Hyves, a popular network site within The Netherlands on the Internet.

Students who were interested to participate had to fill out an online screening questionnaire to determine eligibility. Participants were only invited to attend an information meeting if they had reported in this online screening that 1) they were aged from 12 up to and including 18 years, 2) they were not subject to major physical health problems (cardiovascular disease, diabetes and/or skin disease), 3) they were smoking at least 7 cigarettes per day, 4) their parents were aware of their smoking behavior, and 5) they were motivated to quit smoking (score 2 or 3 on the question: "How eagerly do you want to be a non-smoker?" using a scale from 0 [*not at all*] to 3 [*very much*]). Participants 1) who were currently using nicotine replacement therapy or other smoking cessation medication, 2) who were pregnant or lactating, and 3) who reported being allergic to patches in general or to any ingredients in the patches were excluded from participation.

An information letter was sent to participants and their parents, together with a letter of consent. The information letter included general information about the study procedure, and parents were informed about the participation of their child in the project. According to the regulations of the medical ethical committee, signed informed consent was obtained from both participants and parents (or legal guardians) if participants were 17 years or younger, and from participants only if they were 18.

Participants attended a 75-minute information meeting (including a short smoking cessation training), which usually took place at school with the exception of a few meetings at the Utrecht University or the Radboud University Nijmegen. In the period between February and May 2011, 47 meetings were organized, which were attended by 3 to 15 participants per meeting. These meetings, chaired by a trained research assistant, consisted of three parts. First, a pre-treatment questionnaire (T0) was filled out, to acquire important background information of the participant (e.g. smoking behavior, attitudes concerning smoking, and factors related to smoking (cessation)). Second, participants received (a) information about the study, (b) a short behavioral intervention aiming at quitting smoking (e.g.