Second Conference on the Regulation of Tobacco Dependence Treatment Products

CONCLUSIONS

27 OCTOBER 2000
BARCELONA
TARGET 12
Reducing Harm from Alcohol, Drugs and Tobacco:

By the year 2015, the adverse health effects from the consumption of addictive substances such as tobacco, alcohol and psychoactive drugs should have been significantly reduced in all Member States.

WORLD HEALTH ORGANIZATION
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Second Conference on the
Regulation of Tobacco
Dependence Treatment Products

CONCLUSIONS

27 OCTOBER 2000
BARCELONA
The World Health Organization Regional Office for Europe held its Second Meeting on the Regulation of Tobacco Dependence Treatment Products in Barcelona on 27 October 2000. The first conference was held in Helsinki on 19, October 1999; a summary of the main conclusions from the Helsinki meeting is attached (Appendix 1). Opening presentations were followed by a brief review of the safety of treatments for tobacco dependence, focusing on nicotine replacement therapy (NRT) and bupropion. The remainder of the programme was devoted to discussing challenges surrounding the regulation of tobacco dependence treatment products in Europe, based on a background discussion paper on the regulation of NRT (McNeill et al 2000).

PUBLIC HEALTH PERSPECTIVE
Tobacco products are responsible for 1.2 million deaths (14% of all deaths) each year in WHO’s European Region. It is predicted that, unless stricter measures are implemented, tobacco products will be responsible for 2 million deaths (20% of all deaths) each year by 2020 (WHO Europe, 1997). The high rate of smoking-attributable morbidity and mortality in cigarette smokers results from the extraordinarily toxic nature of cigarette smoke (Hoffman and Hoffman, 1997), and from the process of nicotine dependence. This dependence both requires and reinforces deep exposure of the lungs to high concentrations of smoke, and sustains this exposure (in most smokers) on a daily basis from adolescence until they develop debilitating tobacco-caused diseases (Peto et al. 1994; Henningfield and Slade, 1998).

Attempts to reduce tobacco-caused disease by preventing future generations from using tobacco products are a cornerstone of the efforts of the WHO and many other governmental and nongovernmental agencies (Joossens, 1999). However, these efforts will have little effect on current mortality trends and are unlikely to significantly reduce tobacco-caused diseases for approximately three to five decades. Until then, the primary way to reduce tobacco-related death and disease is to encourage and assist existing smokers to quit smoking. Many epidemiological studies have shown that the risk of smoking-attributable disease is related to the overall level of tobacco toxin exposure (i.e., cigarettes per day and years of smoking), and that the disease risk can be greatly reduced by stopping smoking (National Cancer Institute, 1996, 1997; Peto and Lopez, 2000). These observations support efforts to aid smoking cessation by promoting treatment for tobacco dependence, as well as efforts to reduce tobacco toxin exposure in those who are unable or unwilling to quit smoking. In principle, achievement of these goals while simultaneously increasing the effectiveness of prevention-oriented efforts is not only desirable from a public health perspective but appears feasible (United Nations Focal Point on Tobacco or Health, 1997; World Bank, 1999).

REGULATORY PERSPECTIVE
Consideration of treatment innovation and improved access to treatment that can reduce tobacco-related disease and mortality must constantly consider state of the art information on issues such as effectiveness and safety. This Barcelona conference did not attempt to address all the issues discussed at Helsinki but focused on treatment innovation and expansion of access to treatment, in the context of the potential benefits of pharmacological treatment relative to continued smoking.

PROCESS
The conference participants included a wide range of experts with expertise in clinical and population-based treatment approaches and public health strategies, and also included representatives of European regulatory agencies and pharmaceutical companies. Six categories of treatment-related issues were actively discussed: effectiveness, safety, access, innovation, new indications, and research. Seventeen conclusions emerged from these discussions and are grouped according to these categories. The order of presentation of the conclusions does not necessarily reflect their priority.
CONCLUSIONS

TREATMENT EFFECTIVENESS

1. Treatment works and is an important component of tobacco control efforts through its support of cessation. The updated United States Public Health Service Clinical Guideline, updated English guidelines, the first European recommendations on the treatment of tobacco dependence, and Society for Research on Nicotine and Tobacco treatment database provide strong evidence for the efficacy of behavioural support and pharmacotherapy, mainly NRT and bupropion, in the treatment of tobacco dependence (Fiore et al., 2000; West et al. 2000, World Health Organization Partnership Project, 2000; Society for Research on Nicotine and Tobacco, 2000). These reviews confirm earlier analyses which concluded that all NRT products and bupropion approximately double abstinence rates, thereby providing effective treatment of the WHO ICD10 disorder, Tobacco Dependence (World Health Organization, 1992). These medications alleviate tobacco withdrawal symptoms including craving and thereby provide effective treatment of the WHO ICD10 disorder designated Tobacco Withdrawal. These disorders are designated Nicotine Dependence and Nicotine Withdrawal by the American Psychiatric Association’s Diagnostic and Statistical Manual (American Psychiatric Association, 1994).

2. Treatment can enable tobacco users to quit smoking earlier in their cycle of addiction. The natural history of tobacco dependence is that of a chronic relapsing disorder, with cessation attempts often beginning early in the addiction cycle. Although many tobacco users eventually achieve abstinence without treatment, the reduction in disease risk is greater with earlier cessation (Doll et al 1994). Therefore, all tobacco users should be encouraged to use effective treatment. When evaluating the public health value of any treatment it is important not only to consider whether a smoker might achieve abstinence without the treatment, but also the individual and public health benefits of achieving abstinence earlier in the course of the addiction cycle, thereby further reducing disease risk. Arguments against expanded access to and reimbursement for pharmacotherapy on the basis that many people eventually quit unaided should be set in the context that the majority of smokers who try to stop without help fail.

3. Pharmacological treatment should be offered to young people who become dependent on tobacco. Tobacco dependence can develop in children and adolescents. For addicted young people, educational efforts can be as important as for adults in stimulating cessation. Nonetheless, as with adults, it appears that dependent young people may be increasingly interested in treatment support and that pharmacological treatment may be equally important in enabling them to achieve and sustain abstinence. However, there are marked inconsistencies across Europe in terms of the lower age for using NRT. Preliminary data suggest that the risks of pharmacotherapy do not appear to be substantially greater for youth than for adults, and that such treatment may aid cessation. However, existing safety and efficacy data are limited and research is encouraged on using pharmacotherapy to treat tobacco-dependent youth.

TREATMENT SAFETY

4. Pharmacological treatment products are safe and the safety of such products should be considered in the context of continuing exposure to tobacco. NRT products are remarkably safe (Benowitz 1998) and are rarely abused (Hughes 1998). In fact, the main risk of nicotine in tobacco is that it maintains dependence on and use of tobacco. Bupropion also has a good safety profile although this record has been established under prescription-only availability. The safety profiles of pharmacotherapy support use in specific populations at high acute risk for continuing tobacco use, including pregnant women, youth and patients with cardiovascular disease. When evaluating the risks and benefits of pharmacotherapy it is important that the relatively
small risks associated with these medications should be compared against the known major risks of continued smoking. In addition, unduly restricting access to pharmacotherapy may result in more people continuing to smoke than if such treatment had been more readily available.

5. **Warnings against NRT product use during pregnancy need to be reduced, with advice to consider their use if non-drug approaches have failed.** NRT is considered to represent less of a health risk than continued smoking during pregnancy (Benowitz 1991). In order to reduce the risk of adverse pregnancy outcomes, abstinence has to be achieved as early as possible in the pregnancy because the risk is positively related to the duration of smoking during pregnancy. Therefore, efforts to encourage smoking cessation with and without pharmacotherapy should be made as early in the pregnancy as possible (Fiore et al 2000). When determining the risks and benefits of these medications it is important to note that the risks of NRT use during pregnancy are low compared to tobacco exposure. In acknowledgement of this, France has removed the warning against NRT use in pregnancy. However, additional research on smoking cessation during pregnancy is needed, particularly on innovative approaches such as the use of combination NRT.

6. **Warnings against NRT use in patients with cardiovascular disease need to be reduced.** Pharmacotherapy, including NRT, represents substantially less risk than continued smoking in patients with cardiovascular disease. This population has much to gain by stopping smoking because of the high risks of continued smoking and rapid reduction of risks that accompany cessation. Moreover, existing data suggest that NRT can safely be used in patients with stable cardiovascular disease (Joseph et al, 1996; Benowitz and Gourlay 1997). However, further research should be carried out to investigate the safety of NRT immediately post myocardial infarction as this period is an ideal opportunity for smoking cessation interventions.

**TREATMENT ACCESS**

7. **Access to pharmacological treatment should be increased, but country-specific regulatory issues complicate universal general sales.** The benefits of increased access to NRT are well-established (Shiffman et al 1997), and more rapid implementation of expanded access strategies is encouraged. An important consideration is the wide availability of tobacco products, presenting the paradox of substantially greater access to the disease-causing product than to pharmacological treatment products. However, plans to expand access to pharmacotherapy must consider differences in regulatory approaches in different countries. For example, in some countries general sales could lead to a lack of meaningful oversight of treatment evaluation and professional guidance that enables smokers to identify and appropriately use effective pharmacological treatments.

8. **Expanded access to pharmacological treatment through nonprescription sales in pharmacies and general sales must consider the role of physicians in order to ensure their increased support of treatment.** Practical considerations, such as limits on the time that physicians can dedicate to smoking cessation and the fact that such time is generally not reimbursed, constrains the ability of physicians to serve as primary smoking cessation counsellors. Nonetheless, physicians can serve an important role for their patients by practicing according to basic principles described in clinical guidelines, i.e. assessing dependence, encouraging treatment use, and referring to specialists for more intensive support where appropriate (West et al 2000).

9. **Stimulating cessation activity at the individual level and at the population level requires continuing education to motivate cessation efforts and to encourage access to treatments.** Continuing to increase cessation attempts requires ongoing education to alert smokers to the serious risks of smoking, the benefits of not starting, and the benefits of stopping. Education is needed in many forms, in-
cluding through mass media and stronger cigarette warning labels. Events such as World No Tobacco Day and Quit and Win contests can further increase smoking cessation activity. For smokers striving to quit, an integrated strategy that increases the availability of pharmacotherapy, help lines and self-help materials is important to make treatment more accessible (CDC, 1997).

**TREATMENT INNOVATION**

10. **Product innovation that leads to more acceptable, and perhaps more effective, pharmacological treatment is strongly supported.** There is a need for an expanded array of treatment types (e.g., inhaled nicotine) and indications (e.g., for extended use and harm reduction). However, perceptions that such innovations will meet with resistance from regulators and potentially severe marketing restrictions limits pharmaceutical company investment and commitment. Although regulatory authorities are generally constrained from endorsing treatments that have not been formally submitted for approval, it was suggested that they could stimulate the development of innovative pharmacotherapy and applications by indicating that they will encourage applications, will prioritise reviews of tobacco dependence treatments, and will evaluate these medicines in the context of their potential public health benefits. Maintaining science and evidence-based standards for treatments, while encouraging product development, is a challenge, e.g., “fast track” regulatory approaches could speed up treatment evaluation and approval while retaining appropriate scientific oversight.

**EXPANDED INDICATIONS**

11. **Using NRT to enable temporary abstinence by alleviating withdrawal symptoms (e.g., in workplace settings) supports smoke-free policies.** The onset of nicotine withdrawal symptoms occurs within a few hours of smoking the last cigarette (Parrott et al 1996). There is a strong scientific base for treating withdrawal symptoms and it is important to facilitate efforts to maximise reduced exposure among smokers and nonsmokers. However, in many countries this application is hindered by the regulations that limit NRT use to cessation attempts only. Important research questions include whether treating withdrawal symptoms during temporary abstinence from smoking promotes (by taking steps toward cessation) or undermines quitting (by enabling smokers to cope in smoke-free situations).

12. **Long-term use of pharmacological treatment should be supported by less restrictive labelling.** Many people relapse to smoking after discontinuing pharmacotherapy in compliance with the product labelling and out of fear of long-term medication use that is reinforced by package warning labels. On the other hand, pharmacotherapy should not be used for longer than necessary to achieve long-term abstinence. Finding the balance between supporting use that is long enough to achieve abstinence, but no longer than needed, is complicated and similar to that faced in other areas of medicine, e.g., depression and hypertension, in which it has been increasingly accepted that patients should continue their medications as needed to control the disorder.

13. **Using NRT to support smoking reduction in persons unable to quit is a plausible potential approach to disease reduction.** Many people are unable or unwilling to quit smoking and they are increasingly switching to cigarettes that are advertised or branded as “light” and “low tar.” These cigarettes have not been shown to reduce the risks of smoking compared to their corresponding full strength brands (e.g., Marlboro compared to Marlboro Light). However, as the risk of many smoking-attributable diseases is directly related to the number of cigarettes smoked per day (National Cancer Institute, 1997) and to smoke intake (Wald and Watt, 1997), it is possible that using NRT to assist smoking reduction would result in reduced risk of disease. The risks posed by concomitant NRT use while smoking cigarettes appear relatively small compared to continued unmitigated smoking. However, efficacy data and protocols for implemen-
ting such strategies outside specialist clinics are only beginning to emerge (Bolliger et al 2000) and further research on this application is needed. The effect of smoking reduction on cessation also needs to be evaluated. Allowing concomitant use of NRT with tobacco, as is the case in France, is a step in the direction towards a smoking reduction application.

14. **Warnings against combination NRT use should be removed.** Combinations of NRT products such as nicotine patch to control general withdrawal symptoms and nicotine gum to relieve acute cravings have a strong theoretical basis, and there is a growing research base demonstrating higher abstinence rates with combination treatment (Fiore et al 2000). Such combinations might be particularly for treating heavier smokers. However, warnings against combination use on NRT product labelling may discourage combination NRT use by smokers and the potential advocacy of such use by health professionals who counsel within the bounds of product labelling. Additional research is encouraged to develop further efficacy data and specific guidance on how combination treatment can be most effectively selected and used.

**RESEARCH**

15. **Government and charity-supported research should focus on investigating aspects of the dependence and treatment process that will support their efforts to foster expanded treatment access and innovation.** Evaluating the risks and benefits of innovative treatments requires a substantial knowledge base and a source of empirically based guidance that keeps pace with development within the tobacco industry and pharmaceutical industry. The burden of primary evaluations of safety and efficacy should remain with the medication sponsors.

16. **One major question that will require ongoing attention is how to continue to level the playing field between product research and development for pharmacological treatment and tobacco products, without opening the door to reckless marketing of unproven treatments or products from tobacco companies that have not been properly evaluated.** Key assets in the expansion of pharmacological treatment have been the science base and regulatory framework that have contributed to safety and efficacy, thereby supporting expanded access. However, one drawback is that these evolutionary processes have not kept pace with the growing tobacco epidemic or the ability of the tobacco industry to market new products intended to undermine cessation efforts. On the other hand, care must be taken to not speed the evolution to such an extent as to cause harm by allowing proliferation of insufficiently evaluated products that may carry their own risks; this might undermine the confidence of both smokers and public health officials in pharmacological treatment.

17. **Exploring alternative means of nicotine maintenance for smokers who find smoking cessation or reduction unacceptable merits further consideration and research, although several challenges to implementing such approaches remain.** A major challenge to nicotine maintenance approaches is to investigate whether such approaches would maintain nicotine use in persons who would otherwise have managed to stop using nicotine. Another concern is whether nicotine maintenance products might serve as a new means to initiate nicotine dependence, either in their own right or as entrées to other forms of nicotine delivery. Another challenge is to develop appropriate regulatory strategies that would maintain the standards for purity and safety that are accorded to existing nicotine replacement products.
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APPENDIX 1

Summary of the main conclusions from the Helsinki meeting on
the regulation of tobacco dependence treatment products

1. Treatment of tobacco dependence is essential to reversing
current trends of escalating mortality.

2. Regulations need to be transnational and coordinated with
tobacco product regulation.

3. Treatment works. There is now a strong evidence base
demonstrating that current methods of treatment for tobac-
co dependence are safe and effective.

4. Tobacco dependence treatment is cost effective relative to
other healthcare interventions.

5. Opportunities to purchase cigarettes should increasingly be
opportunities to obtain treatment for tobacco dependence.

6. Diversity of treatment types is needed.

7. Treatment provision should be integrated with tobacco con-
trol policies so that their effects are mutually enhancing.

8. Treatment and prevention efforts go hand in hand.

9. For people who are unable or unwilling to quit tobacco use,
consideration should be given to developing treatments that
reduce their risk of premature mortality.

10. Regulatory authorities need to consider the reality of ubiq-
uitous cigarette availability as they balance the risks and
benefits of treatment medication in the approval process.

11. For treatments with strong safety records, general sales
approvals should be considered as a means of improving
access in a consumer acceptable way.

12. Reimbursement of proven treatments should be considered
to ensure that financial limitations of cigarette smokers do
not pose a major barrier to treatment.

13. Tobacco product regulation, including labelling and adver-
tising should consider its impact on treatment utilisation.

14. European Union Directives should be implemented in a
manner which encourages treatment utilisation.

15. The regulatory process must be guided by the best available
science and the effects tracked so as to maximize health
benefits, minimize unintended consequences, and to there-
by foster self-correction.
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This document provides a synthesis of the conclusions that emerged from the presentations and discussion.

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