RESEARCH PAPER

A prospective study of off-label use of, abuse of, and dependence on nicotine inhaler

J R Hughes, E H Adams, M A Franzon, M K Maguire, J Guary

Objective: To determine the incidence of off-label use of, abuse of, and dependence on prescription nicotine inhaler.

Design: Prospective telephone and internet interviews for six months.

Participants: 535 new inhaler users.

Main outcome: Structured interview about off-label use (that is, use of inhaler for non-cessation reasons or concurrent use of inhaler and cigarettes) and Diagnostic and statistical manual, fourth edition (DSM-IV) and International classification of diseases, 10th edition (ICD-10) criteria for abuse and dependence

Results: Although many used inhaler and cigarettes concurrently at some time (43–55%), few used inhaler for non-cessation reasons (4–9%) and few persisted in off label use (8–16%; 95% confidence interval (CI) 5% to 19%). No participant met ICD-10 criteria for harmful use/abuse (95% CI 0% to 3.3%). Eight subjects (1.4%) appeared to meet DSM-IV or ICD-10 criteria for dependence on inhaler, but none were found dependent in a clinical expert interview (95% CI 0% to 3.3%).

Conclusions: Although transient concurrent use of inhaler and cigarettes often occurs, use for non-cessation reasons, abuse and dependence are rare.

Off-label use, abuse, and dependence have been uncommon with nicotine gum and patch products1 2 even in over-the-counter (OTC) settings.3 Whether this is also the case for the nicotine inhaler has not been tested. Because the inhaler is more similar to a cigarette in appearance and mode of use, abuse/dependence with the inhaler might be greater than that for other oral nicotine replacement therapies (NRTs) such as nicotine gum, lozenge, or microtab. On the other hand, despite its name, the product provides buccal not lung absorption.4 As a result, nicotine absorption is slow and resultant blood concentrations are low, both of which are associated with smaller behavioural effects and less abuse liability.5 Also, the work required to obtain nicotine from the inhaler is much greater than that from smoking. These factors would suggest the inhaler should have little abuse/dependence liability. Currently, many prescribers and smokers believe NRT products are “addicting”.5 7 For example, 55% of smokers believed it was as easy to become addicted to inhaler as to cigarettes.5

In a preclinical abuse liability study, the inhaler did not increase self reported liking or good effects nor increase any increase self reported liking or good effects nor increase any outcomes occurred with nicotine gum in this study.6—9 In a preclinical abuse liability study, the inhaler did not increase self reported liking or good effects nor increase any outcomes occurred with nicotine gum in this study.6—9

Issues in interpreting abuse/dependence data

Discussions of abuse of and dependence on nicotine replacement therapy (NRT) can be misleading because of faulty assumptions, definitions, and misconceptions. For example, concurrent use of NRT and cigarettes on the same day is sometimes interpreted to indicate NRT abuse. In fact, most concurrent use appears to be a transient phenomenon among smokers who are trying to establish abstinence or among abstinent smokers who are on the way to a relapse.10 11 Another example is that some studies equate long term use with dependence on NRT; however, dependence is a clinical syndrome that is defined, not by duration of use, but by specific symptoms.12 13 Thus, some long term users will not be dependent users.

A third example is that sometimes endorsement of a single symptom (for example, “feeling dependent”) is equated with dependence. The accepted definitions of dependence in the American Psychiatric Association’s Diagnostic and statistical manual, fourth edition, text revised (DSM-IV-TR)14 and the World Health Organization’s International classification of diseases, 10th edition (ICD-10)15 require three or more indices because most of those with one or two symptoms do not develop dependence.16 The DSM-IV and ICD-10 also state that a diagnosis requires not just symptom endorsement but also demonstration of clinical significance.13 17 Finally, sometimes dependence on NRT is discussed as if it represented new cases of nicotine dependence, yet actually nicotine dependence has been transferred from the cigarette to NRT.

The purpose of the present study was to estimate the incidence of, abuse of, and dependence on, the nicotine inhaler while avoiding the problems described above. Retrospective studies and spontaneous adverse event reporting can produce biased results; thus, we conducted a prospective, natural history study among smokers initiating a prescription for the inhaler. The study was initiated by two pharmaceutical companies that marketed the inhaler at the
time of the study (Pharmacia Consumer Healthcare (now Pfizer Consumer Healthcare) and McNeil Consumer & Specialty Pharmaceuticals) as part of a US Food and Drug Administration (FDA) required post-marketing plan. The study was funded by grants from the two companies to the first two authors (JRH, EA).

In terms of significance, if we found a substantial amount of abuse and dependence, this would argue against OTC use of inhaler. If we found little, it would argue that prescribers and smokers should not be reluctant to use NRT because of fear of abuse or dependence.

METHODS

Sample size

We initially sought 1000 participants. However, we stopped recruiting after enrolling 553 participants because there were no cases of clinically significant abuse or dependence in these 535 (as described below); thus, it would be very unlikely to detect a clinically significant rate of abuse or dependence if we interviewed the remaining 465. With 553 participants, we had a 95% chance to detect a true incidence of abuse or dependence rate of 0.6% or greater.11

Recruitment

Recruitment occurred between May and November 2000 via several methods. Advertisements described a study of inhaler “use” and did not mention abuse or dependence. Rite Aid Pharmacy obtained permission from consumers who filled inhaler prescriptions to forward their names to us. This provided 181 baseline interviews. McNeil Consumer & Specialty Pharmaceuticals invited inhaler users who called their toll-free customer service number and website to participate (177 baseline interviews). We contacted the Harris Interactive online panel of individuals who have agreed to periodically complete surveys and asked new inhaler users to participate (135 interviews). Other sources included letters from pharmacy chains to inhaler purchasers, established panels of smokers, postings on clinical trial websites, and newspaper ads (176 interviews). The study was approved by an institutional review board. We obtained informed consent either over the telephone or via logins on the Harris Interactive password protected internet site before scheduling the baseline interview. Potential participants were not told this study was funded by pharmaceutical companies but were told their information may be viewed by the US FDA and other US agencies.

Inclusion criteria were: (1) ≥ 18 years of age; (2) comfortable speaking and reading English; (3) purchased inhaler within the past 45 days; (4) no use of other smoking cessation products at the time of enrolment; and (5) not pregnant or nursing. Also, participants must have completed the baseline and one month interviews to be included.

Among participants who began using the inhaler 11–45 days before the baseline interview, we asked about off-label use, abuse, and dependence symptoms during the previous 11–45 days. Among participants who had used the inhaler for < 11 days, we did not do so because we thought it unlikely that significant abuse or dependence symptoms would be evident within this short time period. Outcomes did not significantly differ between participants who entered the trial before (n = 289) or after (n = 384) 11 days.

Nicotine inhaler

The Nicotrol Inhaler (now marketed by Pfizer Consumer Healthcare) is a nicotine inhalation system that consists of a plastic cylinder that delivers a nicotine vapour when warm air is sucked over a porous cartridge in the cylinder.16 Absorption occurs buccally and peak plasma concentrations are typically reached within 15 minutes after inhalation.4 5 The physician prescribing information and patient directions recommend puffing multiple times on a cartridge and using 6–16 cartridges/day for 12 weeks, followed by 12 weeks of tapering (that is, total of up to six months). This dosing produces nicotine concentrations similar to that for nicotine gum.4 6 The most common adverse events (AEs) are upset stomach, nausea, diarrhoea, and hiccups and these lead to medication discontinuance in < 5% of users.1 10 Like other NRTs, the inhaler doubles long term quit rates.10 The incidence of AEs with the inhaler is similar to that for gum, lozenge, and patch.17 In the USA, where this study was conducted, the inhaler is available only via prescription.

Interview procedures

Harris Interactive, a national survey company, completed interviews either via a computer-assisted telephone interview (CATI) (n = 358) or via the Harris Interactive internet site (n = 177). Outcomes did not differ significantly between these two formats. The Harris interviewers for the phone interviews had been trained to the international ISO 9002 quality standards (www.iso.ch/iso/en/ISOOnline). All interviewers completed three days of training in use of the computer system, verbatims, phrases, callbacks, and mock interviews.

We conducted the baseline survey within 72 hours of consent. We then conducted one, three, six, and seven month follow up interviews (± 2 weeks). We dropped participants who reported not using the inhaler at two consecutive interviews because it is impossible to misuse, abuse, or be dependent on inhaler if one is not using it. This was a major reason for loss of participants over time. We did not query about abuse and dependence upon a second round of inhaler use because we were interested in the incidence of disorders on a given episode of inhaler use. Thus, most of the reduced sample size over time is from non-use of inhaler, not lost to follow up. We did not provide any treatment nor give any advice about continuation or amount of inhaler use. Participants were reimbursed $10 for each interview.

Survey instrument and definitions of terms

The survey asked about demographics, current and past tobacco and inhaler use, adverse events from inhaler, and criteria for: major outcomes: off-label use, abuse, and dependence (see appendix). Off-label use (that is, misuse) is not defined in either the DSM-IV or ICD-10 nosologies, but commonly refers to repeated use of the drug for purposes other than that intended by the manufacturer or prescriber.18 We defined off-label use of inhaler as either (1) use of the inhaler for reasons other than cessation or (2) concurrent use of inhaler and cigarettes on the same day. To minimise false positives caused by transient episodes of off-label use (for example, smoking one cigarette on one day of inhaler use), off-label use had to occur at least weekly for at least a month. Abuse and dependence were assessed using an adaptation of the DSM-IV and ICD-10 generic criteria to determine substance related disorders. In the DSM-IV, abuse is defined as repeated use of the drug that causes social, legal, interpersonal, or occupational problems; however, health problems from drug use are not included in this definition.12 A result nicotine abuse is rare and is not included in DSM-IV.12 13 In the ICD-10,13 the term harmful use is used instead of abuse and this includes social, legal, interpersonal, or occupational problems but also includes health related problems and could apply to nicotine. Thus, our study examined ICD-10 harmful use and defined this as endorsement of either of two ICD-10 harmful use symptoms (see appendix). To further examine harm from inhaler, we used the standard US FDA method to ask about AEs...
results

subject flow

among the 895 volunteers who consented to the study, 673 completed the first interview and 353 (60%) completed both the first and one month interview and were designated participants. at three months, 364 completed the interview, and at six months 234 completed the interview. at the time of termination of the study, we had contacted all possible participants for six months interviews, but only a small number for seven month follow ups. thus, this report focuses on the data through six months.

one major reason for loss of participants over time was that we did not contact participants who were no longer using inhaler on two consecutive contacts and thus could not be currently abusing or dependent on inhaler. among all the scheduled interviews for those who either were using or had recently used the inhaler, the response rate was 77%—that is, a non-response rate of 23% because of refusals, inability to locate, etc. these non-respondents were similar to respondents on sex, race, education, cigarettes/day, age started smoking, and fagerstrom test for nicotine dependence (ftnd). non-respondents were younger (42 v 50 years old); however, age was not related to the probability of dependence or abuse among respondents. the total completion rate, including those we dropped for non-use of inhaler and non-respondents, was 47%. internet participants completed all surveys at a lower rate than did telephone participants (64% v 81%, p < 0.05); however, the off-label, abuse, and dependence results from the internet and phone interviews did not differ.

participant characteristics

the modal smoker was a middle aged, white woman with some college education who smoked slightly more than a pack of cigarettes/day (table 1). our sample was comparable to that found in prior surveys of prescription gum and patch users,23 except our sample was more educated. as expected with treatment seekers, our sample was older, more female, and more educated as well as heavier smokers compared to national norms of smokers who have tried to quit in the last year.24

during the study, <3% of participants used either another medication or some form of counselling for smoking cessation. at the one month follow up 91% of all participants were currently using the inhaler, and at six month 13% of all who began the study were currently using the inhaler. among those who used inhaler for six months, the average number of cartridges declined slightly from 2.8/day at one month follow up to 2.3/day at six month follow up.

off-label use

eight per cent of participants initially purchased inhaler for a non-cessation reason and 10% did so at some point during the study (table 2). most of this non-cessation use (8.4%) was to reduce rather than to stop smoking. at any given follow up, 43–55% of users reported at least one instance of use of inhaler and cigarettes on the same day since the last

<table>
<thead>
<tr>
<th>table 1</th>
<th>mean (se) or prevalence of participant characteristics</th>
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<tbody>
<tr>
<td></td>
<td>current sample</td>
</tr>
<tr>
<td>age (years)</td>
<td>44 (14)</td>
</tr>
<tr>
<td>women (%)</td>
<td>63</td>
</tr>
<tr>
<td>white (%)</td>
<td>84</td>
</tr>
<tr>
<td>any college (%)</td>
<td>68</td>
</tr>
<tr>
<td>cigs/day</td>
<td>22</td>
</tr>
<tr>
<td>age started smoking</td>
<td>17</td>
</tr>
<tr>
<td>ftnd</td>
<td>5.3</td>
</tr>
</tbody>
</table>

*from prescription data in shiffman et al.23
†from the national health interview survey.24
ftnd, fagerstrom test for nicotine dependence.

<table>
<thead>
<tr>
<th>table 2</th>
<th>incidence (95% confidence intervals) of endorsing items or meeting criteria for off-label use*</th>
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<tbody>
<tr>
<td></td>
<td>repeated non-cession use</td>
</tr>
<tr>
<td>1 month</td>
<td>4% (n = 535)</td>
</tr>
<tr>
<td>3 months</td>
<td>9% (n = 364)</td>
</tr>
<tr>
<td>6 months</td>
<td>7% (n = 209)</td>
</tr>
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</table>

*see text for limitations to the accuracy of these incidence rates.
†either concurrent use or non-cession use on a repeated basis.

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Dependence
The most commonly endorsed dependence symptoms were tolerance, compulsion to use, withdrawal, and use of more inhaler than intended and these occurred in up to one third of users at some follow ups (table 3). However, across the follow up interviews, the mean and median number of dependence criteria reported was one. At any given follow up interview, about 10% of participants endorsed three or more criteria of either DSM-IV or ICD-10. However, only eight participants (1.4%, 95% CI 0.7% to 2.9%) endorsed three or more criteria that occurred over a one month period. Seven of these consented to an interview by the drug abuse expert. In all seven, the expert concluded there was no clinically significant dependence on the inhaler. In several of the cases, the participant used both cigarettes and inhaler and the expert believed the dependence symptoms were caused by nicotine dependence from cigarettes rather than from the inhaler. The expert reviewed the eighth participant’s information and concluded she was not dependent on the inhaler. Thus, no participants met our criteria of dependence (95% CI 0% to 3.3%).

DISCUSSION
Our major conclusions are: (1) about half of smokers (43–55% depending on follow up) use inhaler and cigarettes concurrently at some time point; (2) a few smokers (7–12%) meet our criteria for off-label use—that is, repeatedly use inhaler and cigarettes concurrently or repeatedly use the inhaler for non-cessation reasons; (3) either no or few smokers (0–3%) meet criteria for harmful use (that is, abuse); and (4) either no or few smokers (0–3%) meet criteria for clinically significant dependence.

Table 3 Incidence of endorsing dependence criteria at each follow up*

<table>
<thead>
<tr>
<th></th>
<th>1 month† (n = 535)</th>
<th>3 months (n = 364)</th>
<th>6 months (n = 209)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolerance</td>
<td>29%</td>
<td>26%</td>
<td>20%</td>
</tr>
<tr>
<td>Withdrawal</td>
<td>26%</td>
<td>25%</td>
<td>20%</td>
</tr>
<tr>
<td>Compulsion to use</td>
<td>28%</td>
<td>20%</td>
<td>18%</td>
</tr>
<tr>
<td>Use more than intended</td>
<td>23%</td>
<td>31%</td>
<td>32%</td>
</tr>
<tr>
<td>Unsuccessful efforts to control use</td>
<td>11%</td>
<td>9%</td>
<td>8%</td>
</tr>
<tr>
<td>Use despite harm</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
</tr>
</tbody>
</table>

*See text for limitations to the accuracy of these incidence rates.
†Some of these symptoms could be due to residual nicotine dependence from cigarettes.

Methodological issues
A major asset of this study is that it was a prospective survey of participants. Also, the sample size of our study (n = 535) gave us a 95% chance of detecting an incidence of off-label, harmful use, and dependence of 0.6% or more. Another asset is that it surveyed smokers in a real world setting. In addition, we used operationalised, well accepted definitions for harmful use (abuse) and dependence. Finally, our use of telephone/internet interviews increased anonymity and decreased demand bias, thereby increasing the probability of endorsement of abuse/dependence items.36

One possible criticism of our study is that we used a variety of recruitment sources, each of which probably had unique biases and contributed to sample heterogeneity. Thus, this is clearly not a population based sample. On the other hand, our ads referred to a study of inhaler “use” and did not mention abuse or dependence, thereby decreasing recruitment bias caused by reluctance to disclose abuse or dependence.

Another possible criticism is that only 60% of those who consented completed baseline and one month interviews necessary to estimate off-label use, harmful use, or dependence. In addition, among those eligible for follow-up (that is, still using inhaler) we were able to contact only 77%. Thus, we had complete data on only 47% (of those consented—that is, 60% × 77). Although this follow up rate is consistent with other post-marketing prospective studies of NRT using telephone interviews,29 we may have missed cases of abuse or dependence. It is unclear how much this biased our results. Our participants initially were not told this was a study on off-label use and dependence. However, once the one month interview was completed our intent became clear; thus, dropouts before one month were probably not related to a wish to conceal off-label use or dependence but dropouts thereafter could have been. On the other hand, even if the rate of harmful use or dependence among non-respondents was 10-fold higher (that is, 10% compared to < 1% among respondents), then the overall incidence of dependence would still be less than 5%.

Another possible criticism is that the interviews were done over the phone by non-professionals or via the internet, both of which prohibited detailed clarifying questions as in a diagnostic interview. We attempted to minimise this problem by conducting a clinical interview by an expert for all suspected cases. In addition, internet users typically are more educated, wealthy, etc; however, prior studies in smokers surveyed by internet responded to tobacco surveys similar to smokers surveyed by mail.30 In addition, our study found no differences in outcomes between internet and phone surveys.

Finally, although the nicotine inhaler is available OTC in many countries, in the USA it is a prescription item. Abuse or dependence may be greater in an OTC setting than in a prescription setting; however, the switch of nicotine gum to OTC in the USA does not appear to have increased its abuse/dependence liability.31 32

Off-label use
We surveyed two types of off-label use: use for non-cessation reasons, and concurrent use. Use for non-cessation reasons appears to be rare and such use is usually to reduce rather than stop smoking. Almost half of users had at least one occurrence of concurrent use at any given follow up interview; however, little of this persisted. In addition, concurrent users average only a few cigarettes and inhalers per day. Concurrent use appears to occur mostly in smokers who are having difficulty establishing initial abstinence or who are lapsing toward a full relapse.
Harmful use/abuse
Several AEs occurred in a minority of inhaler users but very few developed serious AEs, and the few serious AEs were deemed not related to inhaler use. There were no participants who reported significant AEs and continued using the inhaler—that is, harmful use or abuse. Given that inhaler use rarely causes significant AEs and given that most inhaler users can readily stop inhaler use (see below) it is understandable that harmful use would be rare. Even if harm from inhaler use occurred, like harm from other NRTs, it would likely not be clinically significant and would certainly pale in comparison to cigarettes.

Dependence on inhaler
Several inhaler users reported at least one dependence symptom during their use of inhaler. Thus, if one simply went by the incidence of participants ever endorsing a symptom of dependence, one would conclude dependence is common. However, few users reported three or more of the DSM-IV/ICD-10 criteria for dependence persisting for a month or more and none or very few appeared to have clinically significant dependence. We believe the low incidence of dependence on inhaler is due, in part, to the lower concentrations of nicotine it produces, the relatively effortful puffing that it requires, and the ready availability of a product with greater abuse liability—that is, cigarettes.

Comparison of current results with prior studies
Our results are similar to the prior clinical trial that reported on abuse/dependence liability. In that trial, early on 43% reported some concurrent use (cf 43–55% in our trial); 23% reported a single symptom of dependence—that is, “felt dependent” (cf our 20–30% endorsing one symptom of dependence at same time); and 19% stated they had difficulty quitting (cf our 8–11%). However, this prior trial did not report on how persistent such symptoms were or whether participants would meet formal criteria for abuse or dependence.

Our results are also similar to those in most studies of nicotine gum—the NRT most similar to the inhaler (little is known about the abuse liability of nicotine lozenge, the other similar NRT). In the gum studies, a significant minority of nicotine gum users used cigarettes and gum concurrently, but persistent concurrent use appeared to be rare and harm from such use either did not occur or was rare. Most but not all recent studies of OTC gum have reached similar conclusions. The only study to determine DSM/ICD diagnoses of dependence on nicotine gum did not use clinician verification but only self report, and estimated the incidence of dependence to be < 2%. In comparison, our rate of self reported dependence was also < 2%. In summary, our results are similar to those with nicotine gum—that is, although concurrent use of NRT and cigarettes occurs in some users, harm from and dependence on NRT is rare.

One final caveat about our study is that, although we have presented incidence rates and 95% CIs for our outcomes, given our likely recruitment and retention biases, these rates should not be seen as point estimates. Rather, we believe these rates simply indicate that harmful use and dependence are rare. Better studies would be needed to determine exactly how rare they are.

ACKNOWLEDGEMENTS
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APPENDIX

What this paper adds

The nicotine inhaler is a proven treatment for smoking cessation that is available as a prescription medication in some countries and as a non-prescription medication in others. Because the way inhaler is used is more like smoking than the way other nicotine replacement therapies (NRTs) are used, some have worried that abuse or dependence with the inhaler may be greater than that with other NRTs. We followed 535 US smokers who had recently been prescribed the inhaler and asked about off-label use (using the inhaler and smoking concurrently or using the inhaler for non-cessation reasons), abuse (using the ICD-10 criteria), and dependence (using the DSM-IV and ICD-10 criteria) over the next six months. Many smokers (43–55%) used inhaler and cigarettes on the same day but usually (84–92% of the time) this was transient. No smoker abused the inhaler. Eight smokers (1.4%) self reported the DSM-IV or ICD-10 criteria for dependence, but a clinician who interviewed them did not believe any were dependent on the inhaler. Thus, our results are similar to those with nicotine gum—that is, although concurrent use of NRT and cigarettes occurs in some users, harm from and dependence on NRT is rare.

Definitions of outcomes*

<table>
<thead>
<tr>
<th>Off-label use</th>
<th>Harmful use</th>
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<tbody>
<tr>
<td>Concurrent use</td>
<td>Damage to health (ICD-10)</td>
</tr>
<tr>
<td>Non-cessation use</td>
<td>Use caused or made health problem worse</td>
</tr>
<tr>
<td>Harmful use</td>
<td>Continued use (ICD-10)</td>
</tr>
<tr>
<td>Dependence</td>
<td>Used for &gt;1 month despite harm</td>
</tr>
<tr>
<td>Tolerance (DSM-IV and ICD-10)</td>
<td>Increasing use of cartridge to obtain similar effect or diminishing effect with repeated use</td>
</tr>
<tr>
<td>Withdrawal (DSM-IV and ICD-10)</td>
<td>Four withdrawal symptoms rated as moderate or severe or using cartridge to avoid or relieve withdrawal symptoms</td>
</tr>
<tr>
<td>Compulsive use (ICD-10)</td>
<td>Crawling or strong desire to use</td>
</tr>
<tr>
<td>Use more than intended (DSM-IV and ICD-10)</td>
<td>Probes for loss of control</td>
</tr>
<tr>
<td>Unsuccessful efforts to cut down or stop (DSM-IV and ICD-10)</td>
<td>≥ 2 failed attempts</td>
</tr>
<tr>
<td>Use despite harm (DSM-IV and ICD-10)</td>
<td>Attribute harm to inhaler and continue use</td>
</tr>
</tbody>
</table>

REFERENCES
The Lighter Side

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