



Nicotine Replacement Therapy

The CDER Experience

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Questions

1. What information does CDER have for the safety of long-term* use of Nicotine Replacement Therapies (NRTs)?
2. What experience or information does CDER have on accidental ingestion or misuse of NRT products when the products became available OTC – particularly involving children <18 years?

*For the purpose of this presentation “long-term” use refers to use beyond the time recommended on product labeling

Background

1. NRTs were approved as drugs.
2. NRTs are not approved for use by people < 18 years old. Any use in this age group is off-label.
3. These products were studied and approved as temporary aids to help people quit smoking. Though we know it occurs, the products were not approved for long term use.

Background (cont.)

4. The original NDA submissions included very little non-clinical data other than published literature.

The effects of nicotine were known. Since NRTs were to be used short term so smokers could quit, it was presumed NRTs used in this way would be less toxic than continuing to smoke.

5. There are limited data on long term use of NRTs.
6. Data are inadequate comparing the safety of long term use of NRT versus not smoking.

Definitions

- Adverse Event: Any untoward medical occurrence associated with the use of a drug, whether or not it is considered drug related
- Serious Adverse Event: Any adverse event that results in one of the following outcomes:
 - Death
 - Life threatening illness
 - In-patient hospitalization or prolonging current stay
 - Persistent of significant disability/incapacity
 - Congenital anomaly/birth defect
 - Important medical events – based on appropriate medical judgment

Sources of Available Safety Data

1. Data presented to FDA to support product approval
 - All were approved as prescription products initially except the lozenges.
2. Data acquired since product approval
 - a. Submitted to FDA as postmarketing data
 - b. Safety updates as part of Prescription to OTC switch
3. Data presented at NRT workshop Oct 2010

Data from published literature, the FDA Adverse Event (AERS) database and the controlled substance database will not be discussed in this presentation



Data Supporting Initial Product Approval

Nicotine Gum 2 mg

Approved Rx 1984

- Pivotal Study: 143 subjects for 6 weeks
- Supportive Study: ~1225 subjects for 6 weeks to 6 months
- No serious treatment related Adverse Events (AEs)
- Common AEs: oral ulcers (active and placebo), nausea, jaw ache, hiccups, insomnia, anorexia, dizziness, headache
- Four studies looked for cardiac effects – no significant cardiac AEs noted

Nicotine Gum 4 mg

Approved Rx 1991

- Pivotal Study: 488 subjects for 6 weeks
- Supportive Study: >550 subjects for 6 weeks; drug available for 2 years (documented use by 5 subjects)
- No serious treatment related AEs
- 4 mg users had more AEs than 2 mg users – primarily dyspepsia, nausea, and hiccups
- Safety Review: 1769 AEs reported to FDA from 1984 to 1990 for 2 mg gum; 68 serious and 27 deaths but none believed related by reporting physician or FDA

Nicotine Patches

Approved Rx 1991 – 1992

- Several products and various strengths
- 2217 Subjects studied
- Studies ranged from 6 – 12 weeks
- No serious treatment related AEs
- Most common AEs: skin irritation (active and placebo), itching, headache, insomnia, dizziness, abnormal dreams, dyspepsia, anxiety, and nausea

Nicotine Nasal Spray

Approved Rx 1996

- Pivotal Studies: 369 subjects treated for 3 months at full dose and 3 months taper
- 241 subjects had drug available for 2 years
- No serious treatment related AEs; nasal irritation was noted in most subjects (declined with continued use)
- Common AEs: throat irritation, nasal congestion, taste perversion, eye irritation, epistaxis, hoarseness, cough, and pharyngitis
- Nasal ulcers were noted in long term users
- Feelings of dependence noted (32% active vs. 13% placebo)

Nicotine Inhaler

Approved Rx 1997

- Pivotal Studies: 489 subjects; 3 months full dose, 3 months taper
- Supportive Studies: 241 subjects; same regimen
- Supplemental Studies: 415 subjects treated 3 months full dose then drug available but smoking allowed (215 – 12 months, 200 – 18 months)
- No serious treatment related AEs
- Most common AE: flu-like symptoms;
- Other frequent AEs: mouth/throat irritation, headache, nausea, anxiety, dyspepsia, cough, pharyngitis, rhinitis, taste perversion and tongue soreness

Nicotine Lozenge 2 mg and 4 mg

Approved OTC 2002

- Pivotal Studies: 2 mg – 459 subjects, 4 mg - 450 subjects
- Treated for 6 weeks, drug available for 6 months – 25% used
- No serious treatment related AEs
- Common AEs: headache, nausea, pharyngitis, flatulence, heartburn, diarrhea, and hiccups

Nicotine Mini Lozenge 2 mg and 4 mg

Approved OTC 2009

- No new efficacy studies; Sponsor conducted BE trials and post-marketing safety review of lozenge and gum
- Specific review for events related to mouth and throat – no unexpected findings except increased reports of nausea and hiccups; no increase in oral irritation
- No serious or unlabeled AEs in the BE trials
- Common AEs: nausea and GI symptoms, headache, dizziness, and dry mouth

Nicotine Mini Lozenge 2 mg and 4 mg

Post-marketing safety review data

- In spite of labeling, data from multiple sources including AERS show extended use of NRTs occurs – this may be more of a problem with the gum
- There were >30,000 AE reports for nicotine polacrilex through 8/31/08 and only 4 were considered serious
- Overall: Gum and lozenge well tolerated; lozenge has more GI AEs; no unexpected findings



Additional Safety Data Reviewed by FDA

Nicotine Gum 2 mg and 4 mg

Rx to OTC Switch: 1996

- Actual Use enrollees who quit were followed up to one year after study completion; 4-6% were still using gum at 6 months and 3% at 12 months
- Post-Approval study comparing abuse liability of mint gum to original flavor, smoking, and d-amphetamine showed less liability for mint flavor than d-amphetamine and no greater liability than original flavor
- Three other studies evaluated adolescents and different gum flavors finding no suggestion that gum is a form of nicotine delivery that appeals to youth

Nicotine Patches

Rx to OTC Switch: 1996 – 2002

- Actual Use Studies performed; patients treated per labeling and followed 6 months to 1 year; Average duration of use was 6.1 weeks; most used < 2 months
- Poison Control Center data reviewed at the time of each switch and consistently showed low levels of abuse and misuse; few reports of accidental misuse in pediatrics or adolescents were seen – effects were usually minor
- Postmarketing experience concerning residual drug in the patches and product disposal showed disposal directions were adequate and accidental poisoning was not an issue

Nicotine Nasal Spray

Phase 4 Commitment for Rx Approval: 2000

- Abuse evaluation: from 6/98 – 7/99, no reports of misuse or abuse; student survey showed low daily use and limited experimental interest
- Poison Control Center monitored 7/96 – 7/99: 83 inquires and 43 exposures; no overdoses or accidental pediatric ingestions
- Cardiac: no increase in AE risk
- Risk of long-term use: 24 month study completed (18 months treatment, 6 month FU); no negative findings on nasal exam and no significant AEs

Safety Data Presented at NRT Workshop, October 2010

Question for Panel 2:

“What is known about the long-term*
safety of nicotine from human studies?”

*Not all the study data presented were from long-term studies

Dr. Paul Newhouse, University of Vermont Center on Aging

Studied effects of transdermal nicotine on memory

- 74 non-smoking subjects with mild cognitive impairment
- Randomized to nicotine patch or placebo for 6 months; then offered nicotine open label extension for 6 months
- 39 nicotine first phase, 67 entered open label (54 completed)
- No withdrawal symptoms at study end
- All drug-related AEs were mild to moderate; similar AEs between active and placebo
- Safe long-term use in basically healthy elderly population

Unpublished Data

Dr. Robert Murray, Vancouver Lung Health Study

- Study on prevention of COPD
- ~6000 recruited, 1987-1989
- No randomization of NRT; Gum given free to study participants and significant others
- 65% of smokers who quit used NRT
- At end of 5 year study, 5% still using NRT (8-10 pieces/day in ex-smokers, ~7 pieces/day in smokers)

Lung Health Study (continued)

- Original paper described 3094 participants using NRT; reported AEs were minor (>70% - no symptoms)
- NRT users had fewer hospitalizations for CV conditions than NRT non-users at every year of the study
- Lung cancer patients were followed for an additional 7.5 years – NRT risk for lung CA not significant; cigarettes clearly significant

Murray RP et al., *N&TR* 2009; 11:1076-1082

Murray RP et al. *CHEST* 1996; 109:438-45

Dr. Anne Joseph University of Minnesota

1. Study: Transdermal nicotine in cardiac patients; 580 patients treated for 10 weeks; noted similar rates of total events including death, MI, angina, arrhythmia, cardiac arrest, and CHF

Joseph AM, et al. *NEJM* 1996; 335:1792 - 1798

2. 2001 Observational Data; 68 hospitals, 653 smokers with first MI; evaluated use or non-use of NRT as risk factor in period prior to MI; showed no association

Kimmel SE et al. *JACC* 2001;37:1297 - 1302

3. 2005 Self-Control case series; looked at relative incidence of MI, CVA, and death in four 14-day periods before and after first Rx for NRT; 33,000 prescriptions for NRT – 860 MIs, 500 CVAs; no evidence of event risk with NRT

Hubbard R, et al. *Tob Control* 2005;14:416 - 421

Summary

1. Though we are aware long-term use occurs, the number of subjects exposed to long-term NRTs in clinical trials is small. The numbers are inadequate to support labeling these products as safe for long-term use.
2. OTC NRTs (gum and lozenges) do not seem to pose a significant risk of misuse or abuse among adolescents. We don't know how other formulations would be used. Any use in adolescents is off label.
3. No NRT product has a “reduce to quit” indication.