Long-term Medicinal Nicotine Use after Smoking Cessation

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Tobacco use as a chronic condition
- Is this really a Novel idea?

- Consideration of long-term medicinal nicotine has to do with how one *views* tobacco use (not just about efficacy and safety)

- “Tobacco dependence is a chronic condition that often requires repeated interventions.”
  - 2000 US PHS Guidelines

- Cure?
  - Is tobacco dependence an “acute illness” that we cure with a single course of therapy? - NO

- Treat
  - Chronic relapsing condition
  - *Ongoing* medication and behavioral treatment is sometimes (not always) needed
Comparative treatment efficacy for chronic conditions

<table>
<thead>
<tr>
<th>Chronic condition</th>
<th>Measurable outcome</th>
<th>Successful treatment rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Systolic and diastolic blood pressure</td>
<td>27% (Chobanian, 2003)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Hemoglobin A1C</td>
<td>40% (Hayward, 1997)</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>Abstinence</td>
<td>25-35% (Fiore, 2008)</td>
</tr>
</tbody>
</table>
Cost effectiveness
– Primary Cardiovascular Prevention

- Tobacco treatment: $3,500
- Hypertension treatment: $11,300
- Cholesterol treatment: $65,500

$ $$$ / year life saved
## Comparing Treatments for the Leading Causes of Preventable Death in the U.S.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Diabetes</th>
<th>Tobacco Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence in adult U.S. population</td>
<td>7%</td>
<td>23%</td>
</tr>
<tr>
<td>Causes multiple complications</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Effective approved medications</td>
<td>Sulfonylureas, metformin, thiazolidinediones, exenatide, sitagliptin, insulin, others</td>
<td>NRT (patch, gum, lozenge, inhaler, nasal spray), bupropion, varenicline</td>
</tr>
<tr>
<td>Odds of achieving treatment goals with Medications</td>
<td>Approximately 2-fold increase in achieving hemoglobin A1c &lt; 7%</td>
<td>Approximately 2-fold increase in abstinence</td>
</tr>
<tr>
<td>Effectiveness of single medication treatment</td>
<td>24% reach A1c level &lt; 7% long-term</td>
<td>20-25% long-term abstinence with single NRT</td>
</tr>
<tr>
<td>Combining multiple medications may be beneficial</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Optimal treatment combines behavioral component with medications</td>
<td>Yes (diet and exercise)</td>
<td>Yes (e.g., substitution of behaviors, trigger avoidance, coping skills)</td>
</tr>
<tr>
<td>Classification of condition by insurers</td>
<td>Medical</td>
<td>Unclear (possibly medical illness, mental/behavioral health, substance abuse, preventive care)</td>
</tr>
<tr>
<td>Effective treatment is universally covered by insurance plans</td>
<td>Yes (including occasional specialized case management)</td>
<td>No (often no coverage or available to employers at higher premium)</td>
</tr>
<tr>
<td>Medications typically paid for as long as the condition exists (i.e., no limit on duration of treatment)</td>
<td>Yes</td>
<td>No (often limited to 3–6 mo of therapy)</td>
</tr>
</tbody>
</table>
Comparative Coverage for Cardiovascular Risk Factor Treatment

- Hypertension - Yes
- Diabetes - Yes
- High Cholesterol - Yes
- Tobacco – Variable (despite efficacy and cost-effectiveness)
  - In my practice – this diagnosis has the most denials, PA’s, limits on combinations and duration
We should want tobacco dependence treatment to be just like other chronic medical conditions? BUT...

What?

• Coverage for treatment
  – Medications and counseling not universally covered, often require prior authorization, have lifetime limits of therapy, require concurrent counseling to agree to cover meds, combination medications not often covered

• Duration of treatment
  – Existing “cookbook” limits (12 weeks) – not “as clinically indicated” as with other chronic conditions

Why?

• Stigma
  – Smokers “do it to themselves” – no appreciation for addiction
  – Who are the remaining smokers? Those with little voice - Low SES; mentally-ill

• Treatment Identity
  – Is it medical, behavioral health, addiction, preventive service?

• Policy/Indication – how we view tobacco use
What is the GOAL of treatment?

- Reduce Death
- Reduce Illness
- Reduce Harm to Others
- Reduce/Change Smoking Behavior
- Reduce Addiction
- Reduce Cost

- Specific Goal may impact methods and therapies considered
  - If Goal is less disease, death, and harm to others, long-term nicotine use is a consideration
Continued nicotine use

• Why do people continue to use nicotine?
  – Reward
  – Alleviation of withdrawal and cravings
  – Prevent lapses

• People will continue to get nicotine
  – Restriction of NRT favors continuation of the most hazardous form of nicotine delivery

• Advantages of less harmful forms of nicotine
  – Reduced harm to the individual
  – Reduced harm to others (ETS)
    • No “second-hand patch” effect
Possible tobacco treatment scenarios

• Abstinence
  – Best case – Complete elimination of tobacco caused harm with no long-term risks

• Reduction
  – Lowering of harm from significant reduction of exposure to toxins
    • Still exposed to dangerous toxins
      – Zero safety threshold for some diseases (cancer)
      – Steep dose/disease curve for others (CV disease)

• Long term nicotine substitution
  – 95% or more reduction in risk
  – Concerns
    • Small potential physiological effect of nicotine
      – BP, HR, vascular tone (cardiovascular concerns)
    • Carcinogenic potential
    • Perpetuates addiction
    • Cost
Risk/benefit of long-term medicinal nicotine

• Tobacco smoke
  – Nicotine at high doses
  – Nicotine at rapid arterial peaks
  – 7,000 other chemicals including CO, carcinogens, and pro-clotting agents
  – Proven deadly in numerous studies

• Nicotine medications
  – Nicotine in its safest form
  – Lower levels
  – Slower absorption
  – Proven safe in clinical studies
  – 30 years of use in the population
    • Unlikely to develop unexpected health or abuse issues
Long-term medicinal nicotine rationale

- Nicotine withdrawal occurs shortly after quitting and peaks fairly soon during the course of a quit attempt.
- However, many smokers continue to report cravings long after quitting, and relapse in distant weeks is common.
- Providing NRT beyond the manufacturers’ suggested 12-week treatment period may provide additional efficacy.

- In 2010, the U.K. Medicines and Healthcare Products Regulatory Agency extended the indication for NRT to long-term use.
  - Did not focus on long-term adverse effects.
Prevalence of long-term medicinal nicotine use

- English survey 9,224 people; Long-term (≥ 3 months) NRT use was 5.0% (95% CI = 4.6-5.4) (Silla, 2014)
- More likely:
  - Older
  - Non-manual occupations
  - Women
  - More addicted
- Incidence of long-term NRT use in ex-smokers after quitting smoking is 1–15% (Hajek, 1998; Hajek, 2007; Shiffman, 2003)
- Study of COPD patients (3,923), 15% of quitters and 5% of smokers continued to use NRT after 5 years (Murray, 1998).
Efficacy of long-term medicinal nicotine

- 568 smokers; 24 weeks patch better than 8 weeks (31.6% vs. 20.3% abstinence at 24 weeks and better recovery from lapses) (Schnoll, 2009)
- 525 smokers; 6 months patch superior to 8 weeks (OR 1.70 [1.03-2.81]; P = .04) but 12 months not additionally better (OR 1.17 [0.69-1.98]; P = .57) (Schnoll, 2015)
  - Smokers may have difficulty adhering to patch treatment regimen for 1 year
  - Subgroups of smokers may benefit from long-term treatment (high levels of dependence), and future studies should explore smoker characteristics that may predict better therapeutic response to long-term patch treatment
- Measurable benefits in studies of 12 to 18 months of continued NRT use for relapse prevention (Agboola, 2010) and suggests use is cost effective (Coleman, 2010).
Lack of efficacy for long-term medicinal nicotine

- 26 weeks patch vs. 12 weeks
  - Similar continuous abstinence at 6 months (Tonneson, 1999)
- Nicotine gum (Hall, 2009) for up to one year
  - Similar 7-day point abstinence at six month (56% vs. 54%), one year (41% vs. 33%) or two year follow-up (40% vs. 36%).
  - Average gum use was 3 months or less, despite its availability
- Choice of multiple NRT products, including combination (Joseph, 2011)
  - One year vs. 8 weeks - no significant differences (30% vs. 24% prolonged abstinence)
  - Multivariate model showed extended duration resulted in a 74% increase odds of quitting
  - Significant increase in quit attempts and treatment engagement
Safety of long-term medicinal nicotine

- Data on long-term NRT beyond 3 months are relatively limited, but generally accepted necessary in some successful quitters to avoid relapse to smoking.
- Safe in terms of levels of nicotine delivered (Shahab, 2014) and associated toxicity (Benowitz, 1997; Hubbard, 2005)
Cancer concerns for medicinal nicotine

• Nicotine is not considered to be a carcinogen (see Shields, 2011)
  – In vitro and animal studies - nicotine may play a role in tumor promotion through angiogenesis and inhibition of apoptosis
  – Animal studies do not indicate that nicotine alone is tumorigenic

• Lung Health Study - 5-year RCT with 7 year follow-up (Murray, 2009)
  – No difference for risk of lung (or other) cancers, but the study was small
  – Does not indicate a strong role for nicotine in promoting cancer in humans

• Lung cancer risk not increased for exclusive smokeless tobacco users (Boffetta, 2005; Luo, 2007)
  – Some insight into increased lung cancer risk for long-term NRT
Cardiovascular concerns for medicinal nicotine

• Nicotine pharmacotherapy use outweigh the risks, even among smokers with stable heart disease
• Cigarette smoking produces a higher peak and average dose of nicotine than does NRT
• Meta-analysis adverse events (Mills, 2010) across 92 RCTs and 28 observational studies
  – Possible excess of chest pain and heart palpitations among users of NRT compared with placebo groups
  – Only clinically significant adverse event from the trials and constitutes an extremely rare event (2.5% in the NRT group vs. 1.4% in the control group)
Addiction concerns for medicinal nicotine

• Currently approved NRT formulations have a low abuse liability (West, 2000) as all products deliver less nicotine, and at much slower rates, as compared to cigarette smoking (Benowitz, 1998)

• Longer-term use of NRT products is uncommon (Hughes, 1991), and long term problematic use (i.e., abuse) is even less common (Hughes, 2004)
Conclusions

• Tobacco use and its treatment needs to be considered in similar fashion to other chronic conditions
  – Tobacco dependence is not acute and is not cured
  – Treatment availability should be on par with diabetes, hypertension, hyperlipidemia treatments – indication, duration, coverage

• Efficacy for long-term medicinal nicotine is mixed overall, but much safer than tobacco use and likely safe overall

• Approval/allowance of long-term medicinal nicotine may be a preferred alternative for a small proportion of NRT users
  – Favors continued use of safest form of nicotine delivery
  – Data not strong for everyone to use long-term medicinal nicotine
  – But, should be available for those who might benefit (high dependence)
  – Will not be used by many, but should be an option for those who need it