Session 6: Are Non-Nutritive Sweeteners Safe? A Look at the Evidence?

Learning Objectives

1. Outline the current evidence regarding the safety of non-nutritive sweeteners
2. Educate patients regarding the potentials benefits and risks of ingesting foods and beverages sweetened with sugar substitutes

Faculty

Judith Wylie-Rosett, EdD, RD
Professor and Division Head for Behavioral and Nutritional Research
Department of Epidemiology and Population Health
Albert Einstein College of Medicine
Bronx, New York

Judith Wylie-Rosett, EdD, RD, is professor of epidemiology and population health and head of the Division of Behavioral and Nutritional Research at Albert Einstein College of Medicine. Dr Wylie-Rosett has served as an investigator in the Diabetes Control and Complications Trial, the Diabetes Prevention Program, the Women’s Health Initiative, and the Trial of Antihypertensive Interventions and Management Study. Her own National Institutes of Health–funded research has addressed resource utilization in weight control. Dr Wylie-Rosett is also associate editor of the journal Diabetes Care. Her publications include over 140 peer-reviewed research papers, over 50 review and practice-based papers, 30 book chapters and four books.

Faculty Financial Disclosure Statement
The presenting faculty reported the following:

Judith Wylie-Rosett, EdD, RD receives grant/research support as an investigator for Kraft and receives honoraria from Unilever and Monsanto as a consultant.

Education Partner Financial Disclosure Statement
The content collaborators at American Society of Nutrition have reported the following:

Richard Kahn, PhD does not have anything to disclose.

FDA-Approved Non-Nutritive Sweetener List

<table>
<thead>
<tr>
<th>Sweetener</th>
<th>Trade Name(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>acesulfame-K</td>
<td>Sweet One, Sunnett</td>
</tr>
<tr>
<td>aspartame</td>
<td>NutraSweet, Equal</td>
</tr>
<tr>
<td>neotame</td>
<td>In products in combination with NutraSweet</td>
</tr>
<tr>
<td>stevia</td>
<td>Truvia, PureVia, Sweet Leaf</td>
</tr>
<tr>
<td>saccharin</td>
<td>Sweet ‘N Low</td>
</tr>
<tr>
<td>sucralose</td>
<td>Splenda</td>
</tr>
</tbody>
</table>
Acronym List

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADI</td>
<td>acceptable daily intake</td>
</tr>
<tr>
<td>GRAS</td>
<td>generally recognized as safe</td>
</tr>
</tbody>
</table>

Suggested Reading List


Pre-Test Question 1

How confident would you be discussing the benefits and downfalls of non-nutritive sweeteners (NNS)?

1. Extremely confident
2. Very confident
3. Moderately confident
4. Slightly confident
5. Not confident at all

Pre-Test Question 2

Which of the following statements is accurate with regard to the increased consumption of NNS from 1965 to 2004?

1. Increased diet soda consumption was associated with an increase in the incidence of bladder cancer.
2. Increased consumption was largely accounted for by the increased intake of NNS from diet soda among adolescents.
3. Increased consumption of NNS was less, per capita, than the increased intake of nutritive sweeteners.
4. Increased consumption was accounted for by an increase in advertising dollars for diet soda.

Pre-Test Question 3

In accordance with FDA warnings, which of the following would you warn patients about with regard to the safety of aspartame?

1) Headaches and seizures occur in individuals who exceed the acceptable daily limit.
2) Aspartame should NOT be consumed by individuals without the enzyme to metabolize phenylalanine.
3) Aspartame can raise methanol levels enough to impair judgment.
4) Aspartame increases requirements for vitamin B12.

Pre-Test Question 4

Longitudinal data from multicenter studies suggest which of the following?

1) The incidence of diabetes and metabolic syndrome is higher in daily diet soda consumers.
2) Report that higher intake of non-nutritive sweeteners intake is associated with higher risk of brain tumors.
3) Results from these studies are used to establish the acceptable intake (ADI).
4) Results from these studies provide evidence that is used to classify a non-nutritive sweetener on the generally recognized as safe (GRAS) list.
Issues
1. Intake trends for non-nutritive sweeteners (NNS)
2. Food & Drug Administration (FDA) procedures to establish the acceptable daily intake (ADI)
3. Examination of chemistry and safety of NNS
4. Evidence review of potential benefits

How Does Perception of Terms Vary?
• Artificial sweeteners
• Sugar substitutes
• Non-nutritive sweeteners
• Low-calorie sweeteners
• High-intensity sweeteners

Consuming Beverage: % of Population

Trends in Per Capita Intake

International Food and Nutrition Council (IFIC) 2010 Consumer Survey
N = 1024
• 40-45% tried to avoid products containing non-nutritive sweeteners
• 41% tried to avoid refined carbohydrates
• 70% tried to avoid sugar
• 22% of those trying to lose/maintain weight (n=788) used non-nutritive sweeteners as strategy

Sources of Beverage Intake of Adults
24-Hour Recall Snapshot
National Health and Nutrition Survey (NHANES) 2005-2006

Sources of Beverage Intake of Children: Age 2-18 Years
24-Hour Recall Snapshot
National Health and Nutrition Survey (NHANES) 2005-2006

Issues
1. Intake trends for non-nutritive sweeteners (NNS)
2. Food & Drug Administration (FDA) procedures to establish the acceptable daily intake (ADI)
3. Examination of chemistry and safety of NNS
   • FDA approved NNS
   • Other NNS
4. Evidence review of potential benefits

The FDA methods for determining the acceptable daily intake include:
1) Testing for toxicity with non-rodents for 1 year.
2) Using national food consumption data to develop prediction models for adverse effects.
3) Human clinical trials conducted by the federal government labs.
4) Surveillance data derived from case reports of adverse effects to the Centers for Disease Control.

FDA Questions to Evaluate New Sweeteners as Food Additives:
- How is the sweetener made?
- What are its properties when it is added to foods or beverages?
- How much of the sweetener will be digested or otherwise absorbed by the body?
- Are certain groups of people likely to be more susceptible than others to the additive?
- Does the sweetener have any known toxic effects, including hereditary disorders or cancer?

Use of Non-Nutritive Ingredients in Candy

- 1906 - Food & Drug Administration (FDA) established
- 1910 - Court Decision permitted addition of harmless non-nutritive ingredients up to .004 of the product
- 1938 to 1963 – Litigation over labeling and use of non-nutritive sweeteners in candy bars
- 1966 – Congress required non-nutritive substances have some practical function (FDA prohibited non-nutritive sweeteners)
- 1992 – FDA reinterpreted the 1966 law to allow non-nutritive sweeteners if generally recognized as safe (GRAS)
How does the FDA determine 100-fold safety level for the ADI for intense sweeteners?

- Genetic toxicity
  - Short-term tests
  - Longer term reproduction studies
    - Potential damage to reproductive system
    - Potential birth defects
- Metabolic and pharmacokinetic studies
- Sub-chronic toxicity
  - Short term tests (usually 90 days in rodents)
  - One year testing in non-rodents
- Chronic (lifetime duration i.e., 24 months, typically) studies of toxicity and carcinogenicity in rodents


**Issues**

1. Intake trends for non-nutritive sweeteners (NNS)
2. Food & Drug Administration (FDA) procedures to establish the acceptable daily intake (ADI)
3. Examination of chemistry and safety of NNS
4. Evidence review of potential benefits

**Saccharin**

- 300 times as sweet as sucrose
- Discovered in 1879
- Increased usage during WWII sugar shortage
- Used in soft drinks, table top sweeteners and foods
- Has a slightly bitter aftertaste
- Is heat stable

Saccharin was banned by FDA in 1970 with subsequent congressional intervention that put it back on the market.

* The FDA requires a cancer warning label from 1972-2000.
* The ADI established by the FDA is 5mg/kg.
* The FDA permits 2 mg per fluid ounce in beverages.

* Same as WHO and Europe ADI

**Aspartame**

- Aspartame is 200 times sweeter than sucrose.
- Aspartame is a methyl ester dipeptide of phenylalanine and aspartic acid.
- Aspartame is digested as a protein, and amino acids are metabolized.
- Aspartame is not stable when heated/not used in cooking.

Aspartame was discovered in 1965 and approved by FDA in 1981.
- Case reports of dizziness and headaches
- Review of concerns about brain tumors were addressed by examining trends prior to the FDA approval of aspartame
- Patients with phenylketonuria (PKU) should avoid aspartame because they lack enzyme to breakdown phenylalanine
- The ADI established by the FDA is 50 mg/kg.

*WHO and EPA set at 40 mg/kg

**Neotame**

- 8,000-13,00 times as sweet as sucrose
- Similar structure to aspartame but dimethylbutyl group prevent enzymatic breakdown
- Is used in combination with other sweeteners in food products


**Acesulfame potassium or Acesulfame-K**

- 200 times as sweet as sucrose
- Discovered 1967 and FDA approval 1988
- Heat stable


**Sucralose**

- 600 times sweeter than sucrose
- Made from sucrose by replacing 3 hydroxyl groups (OH) with chloride (Cl)
- Stable at hot and cold temperatures


**Neotame**

- Discovered 1965 and FDA approval in 2002
- Hydrolyzed to produce methanol but less than found in fruit juice
- ADI is set by FDA at 18 mg/kg*
- Is not subject to enzymatic breakdown to amino acids and is excreted unchanged

*WHO and Europe ADI 1-2 mg/kg

**Acesulfame-K: Safety Considerations**

- Discovered in 1967 and approved by FDA in 1988
- Questions about breast tumors in lab animals
- ADI is set by FDA at 15 mg/kg*
- Approved by FDA for general use except for in meat and poultry

*World Health Organization and Europe ADI 0-40mg/kg

**Sucralose – Safety Consideration**

- Discovered in 1976 and FDA approved in 1998
- Extensive animal testing
- Excreted from the body unchanged in short-term and long term studies
- One Danish study of premature births
- ADI is set by FDA at 5 mg/kg*

*WHO and Europe ADI are 15 mg/kg
Stevia (rebiana)

- Up to 300 times as sweet as sucrose
- Stevia plant leaves were widely used for centuries in South America to sweeten foods and beverages
- Stevioside and rebaudioside - sweet steviol glycosides extracted from the stevia leaf.


Stevia: Safety Considerations

- Used as non-nutritive sweetener in Japan since 1970 and considered a natural sweetener.
- Was available used as herbal supplement/sweetener before FDA approval in 2008
- Controversy surrounding stevia FDA review (? had limited patent potential)
- Some calls for more safety testing
- ADI is set by FDA at 12 mg/kg

United States Versus Canada

Food and Drug Administration

- The six FDA approved non-nutritive sweeteners (Acesulfame-K, Aspartame, Neotame, Saccharin, Stevia and Sucralose).

VERSUS

Health Canada
- Aspartame, Neotame, Sucralose approved for adding to foods.
- Saccharin, Stevia and Cyclamates are approved ONLY for table top use.


Other Reduced Calorie and Calorie-Free Sweeteners

Thaumatin

- Protein (207 amino acids) produced as a natural response by the blossoms and fruit of tropical flowering plant (katemfe) in response to viroid exposure
- 2000 times sweeter than sucrose
- Perception of sweetness builds very slowly.
- Leaves licorice like after-taste at high usage levels
- Highly water-soluble, stable to heating, and stable under acidic conditions
- Approved as a sweetener in European Union, Japan, and Israel
- GRAS classification by FDA as flavoring not sweetener

Sweetener – Supplement not NNS

- Contains 5 calories per packet
- **Ingredients:** Inulin, fructose, natural flavors, probiotics (bacillus coagulans) vitamins and minerals

**Table Top Sweetener**

- Labeled as calorie free (< 5 calorie/serving)
- **Ingredients:** Xylitol, Maltodextrin and less than 0.3% Sucralose for added sweetness.

**Polyols (Sugar Alcohols)**

**Calories Per Gram**

- 3.0 calories/gram hydrogenated starch hydrolysates
- 2.6 calories/gram sorbitol
- 2.4 calories/gram xylitol
- 2.1 calories/gram maltitol
- 2.0 calories/gram isomalt
- 2.0 calories/gram lactitol
- 1.6 calories/gram mannitol
- 0.2 calories/gram erythritol

**Sugar Alcohols (Polyols)**

**Used in ice creams, cookies, puddings, candies & gum**

- Occur as natural plant products and extractions are used as food additives
- Gas and diarrhea via fermentation of carbohydrate not absorbed in small intestines.
- May be labeled as sugar free or no added sugar
- May be labeled as reduced calorie if 25% lower if with sugar
- Not as sweet as sugars (may be combined with non-nutritive sweetener)
- Generally Recognized as Safe (GRAS)

Sweeteners Without FDA Approval

**Cyclamate** BANNED BY FDA IN 1970

- 30-50 times as sweet as sucrose.
- Sodium or calcium salt of cyclamic acid
- Large doses caused bladder cancer in rats.
- Still used as a sweetener in 55 countries.
Brazzein
(potential FDA application)

• Protein extracted from Oubli, the fruit of a West African vine (Pentadiplandra brazzeana Baillon).
• 1000 times as sweet as sucrose
• Will be produced from genetically modified corn because large scale extraction is not feasible.

Dietary Intake and Incidence of Metabolic Syndrome
Hazard Ratio over 9 Years follow-up by Intake Tertile
Atherosclerosis Risk in Communities (ARIC) Study

<table>
<thead>
<tr>
<th>Tertile</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>1.18 (1.07-1.28)</td>
<td>1.17 (1.07-1.28)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td>1.02 (0.94-1.11)</td>
<td>1.09 (0.95-1.23)</td>
<td>0.07</td>
<td></td>
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<tr>
<td>Diet soda</td>
<td>0.00</td>
<td>0.07</td>
<td>0.80</td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>0.79 (0.72-0.88)</td>
<td>1.20 (1.11-1.29)</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>Model 2</td>
<td>1.05 (0.93-1.15)</td>
<td>1.34 (1.24-1.44)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Model 1 was adjusted for age, sex, race, education, center, and total calories.
Model 2 was adjusted for Model 1 plus smoking status, physical activity, and intake of meat, dairy, fruit and vegetables, whole grains and refined grains.


Multiethnic Study of Atherosclerosis (MESA) Baseline Data

<table>
<thead>
<tr>
<th>Intake (N)</th>
<th>Never</th>
<th>Fle</th>
<th>P</th>
<th>Diet Soda (Frequency of servings)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>2,388</td>
<td>478</td>
<td>587</td>
<td>248</td>
</tr>
<tr>
<td>BMI</td>
<td>27.3</td>
<td>28.3</td>
<td>28.5</td>
<td>29.3</td>
</tr>
<tr>
<td>RCI (%)</td>
<td>99.6</td>
<td>97.2</td>
<td>96.1</td>
<td>96.6</td>
</tr>
<tr>
<td>Activity</td>
<td>2.34</td>
<td>2.36</td>
<td>2.34</td>
<td>2.30</td>
</tr>
<tr>
<td>High school degree</td>
<td>88.3%</td>
<td>91.2%</td>
<td>92.7%</td>
<td>96.3%</td>
</tr>
<tr>
<td>White</td>
<td>14.4%</td>
<td>13.9%</td>
<td>14.4%</td>
<td>13.7%</td>
</tr>
<tr>
<td>Asian American</td>
<td>25.4%</td>
<td>25.7%</td>
<td>25.2%</td>
<td>25.3%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>23.7%</td>
<td>28.8%</td>
<td>25.1%</td>
<td>14.9%</td>
</tr>
<tr>
<td>Chinese</td>
<td>46.5%</td>
<td>21.4%</td>
<td>4.8%</td>
<td>4.9%</td>
</tr>
</tbody>
</table>

Incident Diabetes: 5 - 7 Year's Follow-Up

Multiethnic Study of Atherosclerosis (MESA)

Netton JA, et al.

Diabetes Care

2009; 32 (4):688-694

HR: Hazards Ratio
CI: Confidence Interval

Baseline Diet Soda
(Frequency of servings)

<table>
<thead>
<tr>
<th>Rate or Never</th>
<th>&lt; 1/Wk</th>
<th>1-6/Wk</th>
<th>≥ 1/Day</th>
<th>P trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>N Cases</td>
<td>2,961</td>
<td>221</td>
<td>455</td>
<td>914</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.00</td>
<td>1.06</td>
<td>1.39</td>
<td>1.61</td>
</tr>
<tr>
<td>Model 1*</td>
<td>(0.73-1.52)</td>
<td>(1.07-1.80)</td>
<td>(1.17-2.15)</td>
<td>(1.24-2.13)</td>
</tr>
</tbody>
</table>
| Model 2: Adjust Mod 1 +
  intake, activity, smoking, supplements | 1.00   | 1.10   | 1.46    | 1.67    | <.001   |
| Model 3: Adjust Mod 2 +
  waist circumference | 1.00   | 1.00   | 1.23    | 1.40    | <.01    |
| Model 4: Adjust Mod 3 +
  BMI | 1.00   | 0.98   | 1.25    | 1.38    | <.001   |

Meal Study Evidence—NNS Pre-Load Lean and Obese Participants

When consuming stevia and aspartame preloads, participants did not compensate by eating more at either their lunch or dinner meal and reported similar levels of satiety compared to when they consumed the higher calorie sucrose preload.


Systematic Review Evidence

Metabolic Effects of Non-Nutritive Sweeteners in Youth

- Randomized trials in children very limited.
- Lack evidence of either beneficial or adverse effects of non-nutritive sweeteners on metabolic health parameters in children.


Weight reduction concerns

Based on Pavlovian conditioning principles, consumption of non-nutritive sweeteners could result in dissociation between the sweet taste cues and the caloric consequences which could lead to a decrease in the ability of sweet tastes to evoke physiological responses that serve to regulate energy balance.

Switgers SE, et al. Physiol Behav 2010;100:55-62

Practical But Difficult Questions

- Does reducing energy density of sweet beverages and foods have a measurable impact on appetite and energy intakes, as examined both in short-term studies and over a longer period?
- Can reductions in dietary energy density achieved with intense sweeteners really affect body weight control?


Summary

- Most non-nutritive sweeteners are consumed in beverages
- Intake of non-nutritive sweeteners has increased but not as much as sugar sweetened products
- FDA has approved six non-nutritive sweeteners for general use
  - Caution for individuals with phenylketonuria who are missing the enzyme to break down phenylalanine
- Epidemiological studies have shown higher intake of non-nutritive sweeteners is associated with higher body mass intake, diabetes and metabolic syndrome
Conclusions

- Using non-nutritive sweetened beverages as a weight loss strategy needs to be within the context of an overall weight reduction plan.
- Acceptable Daily Intake provides guidance regarding safe usage but is difficult to quantify since the amount of non-nutritive sweeteners in products is not labeled.
- Collaborative counseling approaches can help address patient concerns and goals with respect to using non-nutritive sweeteners.

Post-Test Question 1

How confident would you be discussing the benefits and downsides of non-nutritive sweeteners (NNS)?

1. Extremely confident
2. Very confident
3. Moderately confident
4. Slightly confident
5. Not confident at all

Post-Test Question 2

Which of the following statements is accurate with regard to the increased consumption of NNS from 1965 to 2004?

1. Increased diet soda consumption was associated with an increase in the incidence of bladder cancer.
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Post-Test Question 3

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Post-Test Question 4

Longitudinal data from multicenter studies suggest which of the following?

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4) Results from these studies provide evidence that is used to classify a non-nutritive sweetener on the generally recognized as safe (GRAS) list.