

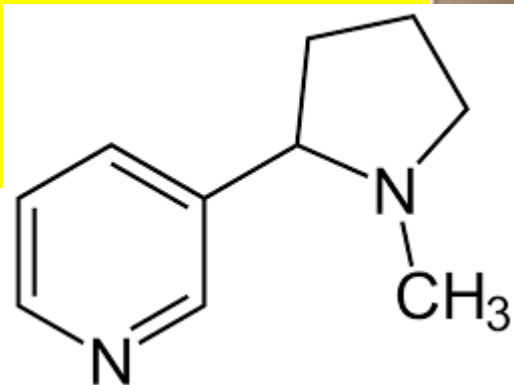
صلى الله عليه وسلم

دکتر بیتا دادپور

متخصص داخلی- فلوشیپ سم شناسی بالینی

دانشیار گروه سم شناسی بالینی
مرکز تحقیقات سم شناسی پزشکی
دانشگاه علوم پزشکی مشهد

Nicotine



History and Epidemiology

- The tobacco plantnative to the Americas
- The principal alkaloid, **nicotine**,primarily derived from.....tobacco plant
- The primary method of nicotine exposure is **cigarette smoking**.



Pharmacology/Pharmacokinetics

- Nicotine is well absorbed from the *respiratory tract, mucosal surfaces, skin, and the intestines*.
- Nicotine from **cigarette or cigar smoke**is carried on inhaled tar particles into the lungswhere **a large alveolar surface** area allows **rapid absorption** into the pulmonary circulation.
- Nicotine readily **crosses the placental barrier**is **secreted in breast milk**.
- Metabolismin the liver..... About **70%** of circulating nicotine is metabolized to **cotine**

- PPL of nicotine and cotinine are influenced *most strongly by individual variations* in clearance.
- Hepatic nicotine metabolism inducible
 - and *nicotine-dependent* individuals*more rapidly* than naïve ones.
- Nicotine metabolism.....race and sex.
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- *Asians* and African Americans metabolize nicotine *more slowly* than Caucasians,and they have *prolonged cotinine clearance* in the urine.

- **Women** metabolize nicotine **faster** than men,

- accelerated by OCP use

- pregnancy,

- ☐ influence of estrogen on CYP2A6 activity



- The half-life of nicotine1 to 4 hours**decreases with repeated nicotine exposure** such as with habitual cigarette smoking.

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- The elimination half-life of **cotinine** is approximately **20 hours** and therefore *urinary cotinine is a more useful marker of nicotine exposure.*
- The apparent elimination half-life of nicotine after transdermal patch removal is longer than that noted with nicotine exposure by other routes,...
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- Cigarette smoking **induces CYP1A2** and accelerates the metabolism of **caffeine, clozapine, olanzapine, theophylline.** *(Nic.?)*

- The LD50 of nicotine has been estimated at about 0.5 to 1 mg/kg in adults.



- Children younger than 6 years of agewho ingest *one or more cigarettes,or three or more cigarette butts*, generally develop symptoms of nicotine toxicity.

Commercial Sources of Nicotine

Source	Content (mg)	Delivered (mg)
1 cigarette (different between...)	10–30	0.05–3
1 cigarette butt	5–7	—
1 cigar	15–40	0.2–1
1 g chewing tobacco)(smokeless tobacco products) periodontal disease, dental cavities, and up to a 48 times greater risk of oropharyngeal cancers	6–8	2–4
1 piece nicotine gum	2 or 4	1–2
1 nicotine patch	8.3–114	5–22 over 16–24 h
1 g snuff (wet)(smokeless tobacco products)	12–16	2–3.5

Cigarettes and Cigars

- Most reports of **acute nicotine toxicity** referable to **cigarette** exposure are associated with cigarette and cigarette butt ingestion, *usually by young children*.
- *Ingesting cigarette soakage water*several suicide cases are reported.
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- IV injection of cigarette soakage is also reported

- Acute nicotine toxicity from **smokeless tobacco** rarely reported in adults.

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- **Rectal administration** of moist snuff **a treatment for migraine headache**significant toxicity in one patient.
- Presumably the relatively **alkaline environment of the rectum** facilitated absorption of a high dose.

PATHOPHYSIOLOGY

- Nicotine's clinical effects dose-dependent.
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- Low doses of nicotinestimulate nicotinic receptors centrally and in autonomic and somatic motor nerve fibers, resulting insympathetic agonism.
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- At toxic concentrations,..... prolonged or excessive nicotinic stimulationultimately leads to receptor blockade, with parasympathetic and neuromuscular-blocking effects.
- At very high dosesseizures.

CLINICAL MANIFESTATIONS

- Exposure to nicotine in low doses comparable to cigarette smoking in nicotine naïve patients produces:
 - *fine tremor, cutaneous vasoconstriction, increased GI motility, nausea, and increases in HR, RR, and BP.*
 - Low-dose nicotine also *increases mental alertness and produces euphoria.*
- Because nicotinepoorly absorbed in the acid environment of the stomach,symptom onset may not occur until 30 to 90 minutes after ingestion of nicotine-containing products.

- Early signs and symptoms of **nicotine toxicity** referable to **nicotinic cholinergic excess**:
 - *increased salivation, N/V, diaphoresis, and diarrhea*within minutes of systemic absorption.
 - Vasoconstriction**pallor and hypertension**.
 - **Tachycardia****nicotine gum** chewing**atrial fibrillation** in several cases.
 - Neurologic signs and symptoms *headache, dizziness, ataxia, confusion, and perceptual distortions*.

- Nicotine is an **irritant** **ingestion of nicotine, ...nicotine gum**, may cause **burning and pain** in the mouth.
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- Similarly,nicotine patches ...dermal irritation.
- *Data from poison centers in the US: most patients with nicotine exposuremild symptomsbenign course.*
- **Vomiting**most common adverse effect reported, although **agitation** also occurs.
- The relative rarity of life threatening symptoms**auto decontamination from vomiting**,
- or ...selection biasunintentional tobacco ingestion by young children

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- Because nicotine is **rapidly metabolized**,.... patients who develop only mild symptoms**recover quickly**.

➤ Most patients recover fully **within 12 hours**.

- But....nicotine toxicity after **transdermal nicotine patch**,..... because a reservoir of drug may persist in the skin after patch removal can serve as a source of ongoing absorption.

- Severe poisoning :
 - biphasic manifestations.... early central stimulation
.....followed by depression.
- Initial signscardiac dysrhythmias, seizures, and muscle fasciculations in addition to the cholinergic features.
- Bradycardia, hypotension, coma and respiratory failure from muscular paralysislater.

- Exposure to **fresh tobacco leaves**GTS, seasickness.
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- *Dizziness, headache, N/V, weakness, diarrhea, abdominal cramps, and chills....*Autonomic instabilityin severe cases.
- Onset of toxicity is **within 3 to 17 hours** after exposure
- Duration of illness**several days**.


- A limited number of case reportspatients poisoned by *imidacloprid or other neonicotinoid pesticides*.
- Many of the clinical manifestationsthe *solvent N-methyl-2-pyrrolidone*, irritant effects on skin and mucosae.
- Intentional imidacloprid ingestions
 - an initial period of drowsiness, disorientation, dizziness, and tachycardia,
 - with subsequent development of fever, vomiting, and leukocytosis.
 - Oral, esophageal, and gastric erosionsupper endoscopy
 - Late-presenting bradycardia and electrolyte abnormalities

DIAGNOSTIC TESTING

- Determination of serum or urinary concentrations of nicotine or its metabolites is **unlikely to be helpful** in the management of the acutely poisoned patient.
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- **Cigarette smokers**serum nicotine concentrations **30 to 50 ng/mL** during the day, but may 100 ng/mL.
- Urinary **cotinine** **a longer detection window** than nicotine,is used to ***document exposure to nicotine containing products***, including exposure to second-hand smoke, ***or to dosage adjustments in nicotine replacement therapy***.
- Conversely, the **absence of cotinine in the urine** may be used to document **abstinence from tobacco products**.

MANAGEMENT

- Most patients with **unintentional or low-dose nicotine** exposures will **not require medical treatment**.
- Patients should be immediately referred for evaluation..... *if they are symptomatic or have ingested* any amount of **nicotine- or neonicotinoid-containing insecticide or fluid**.
- Children who ingest one or more cigarettes or three or more cigarette butts should also be referred for evaluation without delay.
- Patients with **mild or no symptoms** can be **observed for several hours**.....safely discharged homeif no complicating circumstancessuch as ***significant comorbid cardiovascular illness or intent to self-harm***.

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- Patients with **dermal exposure** to wet tobacco **leaves or pesticides** be **undressed completely** and the skin washed thoroughly with **soap and copious amounts of water**.
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 - Personal protective gear should be worn by **medical staff** charged with handling both clothes and patients prior to decontamination.
 - **Symptomatic** patients should have any **nicotine patches** removed immediately and the skin washed with soap and water.

- **Vomiting** is the most commonly reported adverse effect in patients with acute nicotine toxicity, and may limit absorption in some cases.
- *Induction of emesis should be avoided* since it is unlikely to be of added benefit and has the potential for harm.
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- *Orogastric lavage* may be considered in patients who **present immediately** after **large intentional ingestions** of nicotine-containing products.

- AC.....adsorbs nicotine, but the risks of pulmonary aspiration if.....*vomiting, seizure, or depressed level of consciousness.*
- *There is no specific antidote for nicotine toxicity.* Treatment of acute nicotine toxicity is **symptomatic and supportive.**
- Airway protection and respiratory support.
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- **Atropine** may be used to treat symptoms associated with parasympathetic stimulation such as excess salivation, wheezing, or bradycardia.
- conservative

Thank You



PATHOPHYSIOLOGY

- Nicotinemimics the effects of **acetylcholine release** by binding to nicotinic receptors (nAChR)..... in the brain, spinal cord, autonomic ganglia, adrenal medulla, NMJ, and chemoreceptors of the carotid and aortic bodies
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- Activation of nAChR in the CNS directly **stimulates neurotransmitter release**.influx of cations, mostly sodium and calcium.
- Voltage-gated calcium channels are then activated leading to further influx of calcium, and a variety of downstream effects, including depolarization.
- At doses generally produced by cigarette smoking there is stimulation of the reticular activating system and an alerting pattern on electroencephalogram

- Nicotine-stimulated **release of dopamine** occurs in the mesolimbic area, the corpus striatum, the prefrontal cortex, and in the nucleus accumbens;mediator of **nicotine addiction**.
- **NEP, Ach, GABA, serotonin, glutamate, and endorphins** all released by nicotine
 - :
 - Cognitive and mood enhancement
 - Appetite suppression
 - Increased basal energy expenditures
 - Anxiety reduction.

Gum

- Nicotine gum has been available without a prescription as an aid to smoking cessation in the United States since 1996. It is sold in 2 mg and 4 mg strengths per piece.
- Approximately 53% to 72% of the nicotine in the gum is absorbed. It is buffered to an alkaline pH to facilitate buccal absorption. The gum is supposed to be chewed until mouth and throat tingling and a peppery taste develops, signaling nicotine release.
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- The gum is then “parked” in the cheek until the sensation subsides, at which time it may be chewed again to release more drug. If used correctly, serum nicotine concentrations rise gradually to a level slightly lower than normally achieved by cigarette smoking.
- If the gum is swallowed whole, then serum concentrations rise even more slowly because the acidic environment of the stomach delays absorption.
- Conversely, if the gum is chewed vigorously and saliva is swallowed, then nicotine concentrations may rise rapidly and adverse reactions may occur

Lozenges

- Nicotine lozenges containing 2 and 4 mg of nicotine are available for purchase without a prescription in the United States.
- The potential for rapid absorption of nicotine as a bolus dose from chewing the lozenge is a concern.

Transdermal Patches

- Nicotine patches have been FDA approved for purchase without prescription in the United States since 1996.
- Most nicotine transdermal delivery systems are designed to deliver 7, 14, or 21 mg of nicotine over 24 hours.
- Because many patch users have difficulty sleeping, experience vivid dreams, or have nightmares if they wear the patch overnight, systems designed to be applied for only 16 hours are now made.
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- Several reports document consequential nicotine toxicity related to nicotine patch misuse.
- Toxicity may occur in people who continue to smoke cigarettes after beginning therapy with the nicotine patch

- Children have developed symptoms after exploratory self-application of one or more patches to the skin, and concurrent use of multiple patches has been used as a means of suicide.
- Severe toxicity may also occur if patches are punctured—for example, by biting or tearing—thus allowing delivery of excess content.
- The patch reservoirs contain an estimated 36 to 114 mg per patch.
- This amount exceeds the estimated LD50 for nicotine in humans of 1 mg/kg for most children and many adults.

Spray/Inhaler

- A nicotine spray has been available since 1996 to aid efforts at smoking cessation. The most commonly reported adverse effects during initiation of therapy are due to local irritation and include rhinorrhea, lacrimation, sneezing, and nasal and throat irritation.
- One spray delivers 0.5 mg of nicotine and the recommended dose is two sprays every 30 to 60 minutes as needed.
- The absorption is about 50% of the delivered dose and may be diminished or delayed by rhinitis or by α -adrenergic agonist decongestants.⁵⁰ No report of acute nicotine toxicity from nicotine inhalers has been published to date.


Electronic Cigarettes

- Electronic cigarettes, or e-cigarettes, are a relatively new nicotine delivery product now widely available in various strengths and flavors.
- The devices resemble cigarettes and contain a rechargeable battery pack along with a small heating element attached to a reservoir of liquid nicotine.
- An electronic airflow sensor activates the heating element when the user inhales, allowing release of a “puff” of nicotine-containing vapor.
- An FDA analysis of cartridges found that identically labeled products contained variable amounts of nicotine and a number of potentially harmful contaminants.
- The potential for harm is evident, particularly since e-cigarette sales are still unrestricted in many states and large-volume liquid nicotine replacement fluid bottles (used to refill e-cigarette cartridges) are increasingly available.
- The nicotine content of these bottles is substantial.

- Formulations of different strengths are sold; the highest strength preparations may contain over a gram of nicotine per 30mL bottle, raising serious concerns about the risk of both unintentional and intentional toxic exposures.
- Analysis of calls to US poison centers about ecigarette exposures has shown substantial increase between the years 2010 and 2014, with significantly greater adverse effects reported compared to calls about cigarette exposures

Nicotine Receptor Partial Agonists (Varenicline, Cytisine)

- Nicotine receptor partial agonists are used to aid smoking cessation. Theoretically, they work by reducing smoking satisfaction (agonist antagonism effect) while helping to maintain moderate levels of central dopamine release (partial agonist effect).
- Cytisine is a plant-derived xenobiotic with a chemical structure similar to nicotine that has been used in East and Central Europe as a smoking cessation drug since the 1960s under the trade name Tabex.
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- Despite its widespread use, it has not been well studied for its safety, efficacy, pharmacokinetics, and pharmacodynamics in humans

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- Varenicline (marketed as Chantix in the United States and Champix in Europe) was approved as a prescription-only aid to smoking cessation in 2006.
 - Several randomized controlled trials demonstrated efficacy in controlling nicotine cravings and evidence suggests that varenicline increases the probability of successful abstinence from smoking.
 - In 2009, the FDA mandated a black box warning due to an association with increased risk of depression or suicidal behavior.
 - There is still limited experience with effects or outcomes after acute overdose

Plants/Leaves

- Residual moisture or dew drops on tobacco leaves may contain as much as 9 mg of nicotine per 100 mL.
- Sweat wrung out of the shirts worn by workers during tobacco harvest in one study contained up to 98 mg/mL of nicotine.
- Risk factors for GTS include younger age, working in wet tobacco, and a relative lack of work experience.
- These factors may all be related to a lack of nicotine tolerance.
- The use of impermeable garments or other barrier protection is the only protective factor consistently noted to be useful across multiple studies.

Salts (Pesticides)

- Nicotine in the form of tobacco extracts was first reported as effective for pest control in 1690.
- In 1886 a mixture of tobacco and soapsuds was advocated for aphid control, but it was not until 1912 that the first commercial nicotine insecticides were developed.
- Crop dusting with nicotine sulfate began in 1917, although at the time this was mostly accomplished by horse-drawn carriage. The most widely known application of 40% nicotine sulfate, BlackLeaf, was discontinued in 1992.
- Nicotine is still available as a restricted use pesticide, and a 14% preparation of nicotine is still marketed as a greenhouse smoke fumigator.
- Because nicotine pesticides are highly concentrated, the ingestion of even small amounts may produce serious toxicity, including catastrophic brain injury⁷⁵ and death.

Neonicotinoids

- The neonicotinoids are a relatively new class of insecticides with theoretical safety by markedly reducing the affinity for vertebrate nicotinic receptors as compared with those in insects.
- Neonicotinoid compounds include the heterocyclics nithiazine, imidacloprid, thiacloprid, and thiamethoxam; and the acyclics nitenpyram, acetamiprid, clothianidin, and dinotefuran.
- Experience with human poisoning is still limited.

Miscellaneous

- Tobacco has been used for medicinal and therapeutic purposes in many societies for some time.
- Tobacco extract and tobacco smoke enemas were used in the pre-Columbian Americas by many tribes for both medicinal and spiritual purposes.
- They are still recommended by some naturopaths and folk healers as a remedy for constipation, urinary retention, pin worm and “hysterical convulsions.”
- Nicotine has also been recommended as a treatment for migraine, on the basis of its vasoconstrictive properties. Nicotine poisoning has resulted from “therapeutic misadventure” in several documented cases.
- For example, acute nicotine toxicity occurred in an 8 year-old boy after application of a homemade remedy for eczema made from a mixture of tobacco leaves, lime juice, and freeze dried coffee

- A cigar is defined as a roll of tobacco wrapped in leaf tobacco or in a substance that contains tobacco.
- Cigars differ from cigarettes in that **cigarettes are a roll of tobacco wrapped in paper or in a substance that does not contain tobacco.**
- Cigars and pipes differ in design from cigarettes, which are made from tobacco wrapped in thin paper. **Cigars are wrapped in tobacco leaves, and unlike cigarettes, they don't typically have filters.** In pipes, the tobacco sits in a bowl at the end, and a stem connects the bowl to the mouthpiece

- COPD, CVD, pulmonary infections, macular degeneration, and cancers, more than 5 million deaths worldwide per year.

Chronic nicotine exposure cardiovascular damage


- catecholamine release & vasoconstriction
- Promotes angiogenesis
- Neuroteratogenicity,
- Possibly some cancers



- Most patients with nicotine exposure have a benign course,only mild to moderate symptoms*infrequent need for hospitalization.*
- Nicotine rec. partial agonists/antagonistsnew class of drugmimicking *the physiologic effects of nicotine.*
- A 2-year review of poison center data from the California Poison Control System 36 calls regarding human exposures to varenicline (Chantix), which was approved in 2006 by the US FDA as a smoking cessation aid.

- **The neonicotinoids**a relatively new class of insecticideand epidemiologic data about their role in acute pesticide poisoning are still limited.
- **Dermal exposure to tobacco plants** during harvest occupational nicotine toxicityknown as **green tobacco sickness (GTS)**. ...first reported in 1970 among tobacco workers in Florida



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- This may not be an effect of nicotine. IV nicotine ... does not affect theophylline metabolism.
 - Smokers also have *diminished effectiveness of* *opioids, BNZDs, β b, and nifedipine*, and are more likely to fail antacid and H2-blocker therapy for peptic ulcer disease.
 -have also not been clearly linked to nicotine per se.
 - The LD50 of nicotine has been estimated at about *0.5 to 1 mg/kg* in adults.
 - Severe toxicity is reported with ingestion of less than 2 mg in a child