

# 기침을 조절하는 약제: 기전과 분류 중심

한림의대 호흡기내과  
최하영

# Agenda

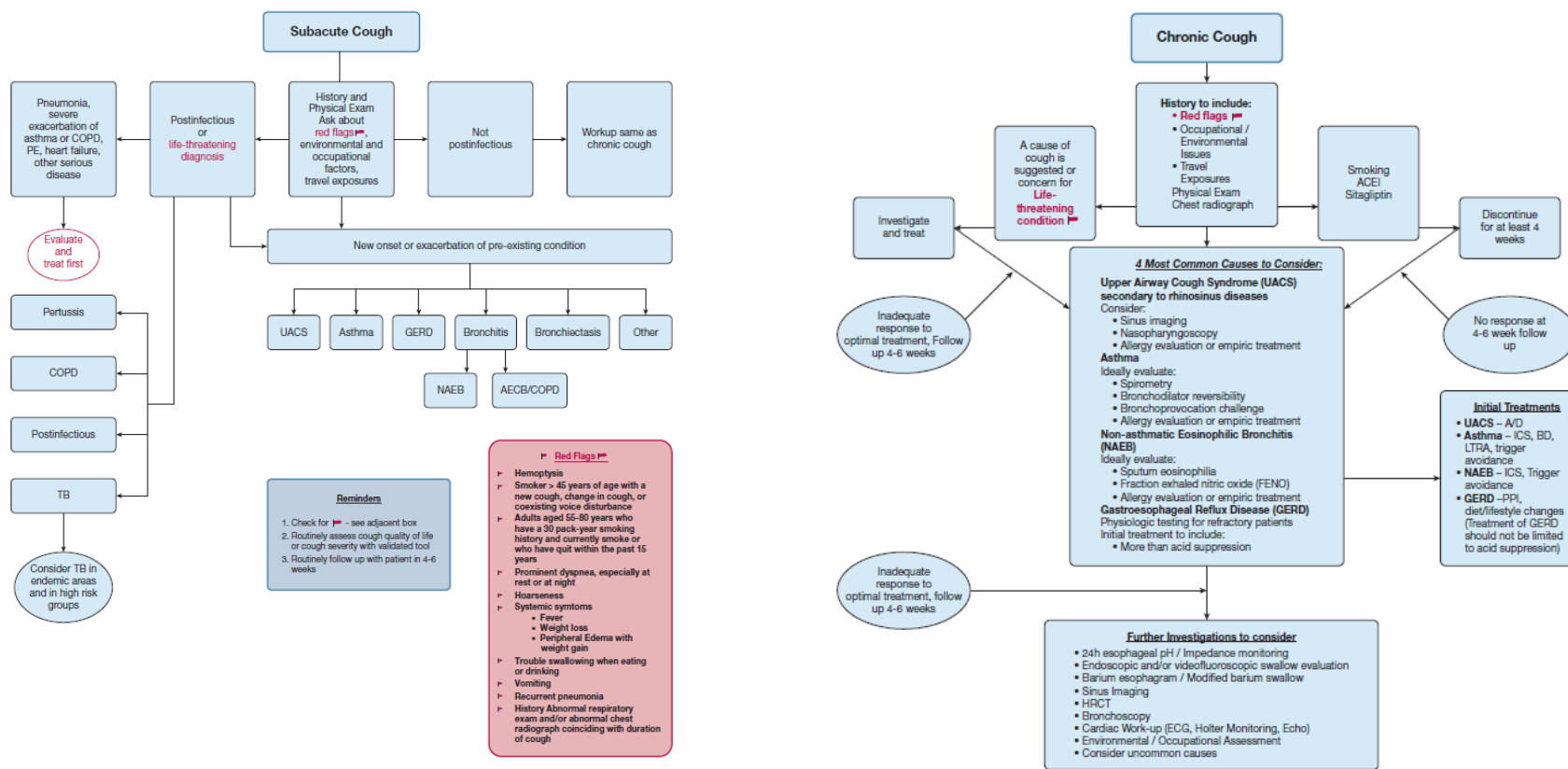
1. Introduction and Physiology of cough
2. Centrally acting antitussive agents
3. Peripherally acting antitussive agents

# Agenda

1. Introduction and Physiology of cough
2. Centrally acting antitussive agents
3. Peripherally acting antitussive agents

# Therapy for cough?

- Specific therapy for etiologies



**Reminders**

1. Check for **Red Flags** - see adjacent box
2. Routinely assess cough quality of life or cough severity with validated tool
3. Routinely follow up with patient in 4-6 weeks

**Red Flags**

- Hemoptysis
- Smoker > 45 years of age with a new cough, change in cough, or coarsening voice disturbance
- Adults aged 55-80 years who have a 30 pack-year smoking history and currently smoke or who have quit within the past 15 years
- Prominent dyspnea, especially at rest or at night
- Hoarseness
- Systemic symptoms
  - Fever
  - Weight loss
  - Peripheral Edema with weight gain
- Trouble swallowing when eating or drinking
- Vomiting
- Recurrent pneumonia
- History Abnormal respiratory exam and/or abnormal chest radiograph coinciding with duration of cough

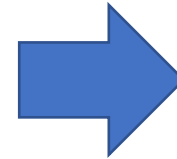
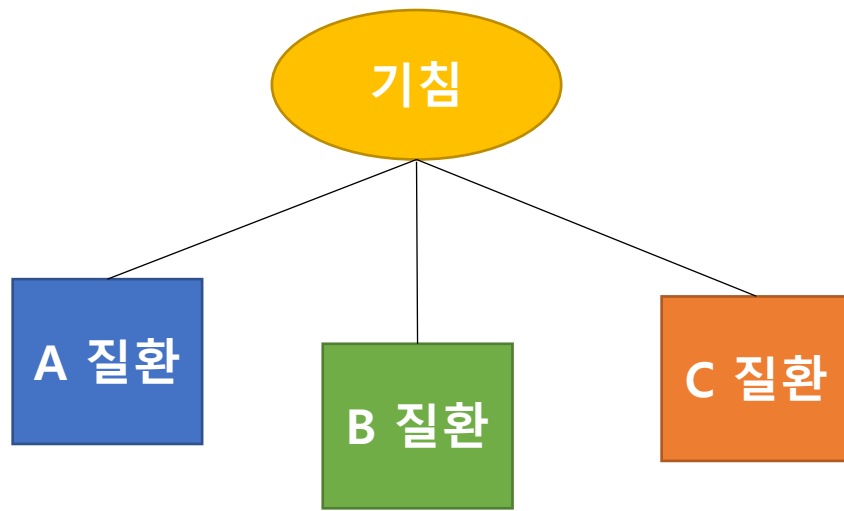


# ERS guidelines on the diagnosis and treatment of chronic cough in adults and children

- Changing concept

- Cough as a symptom of pulmonary disease

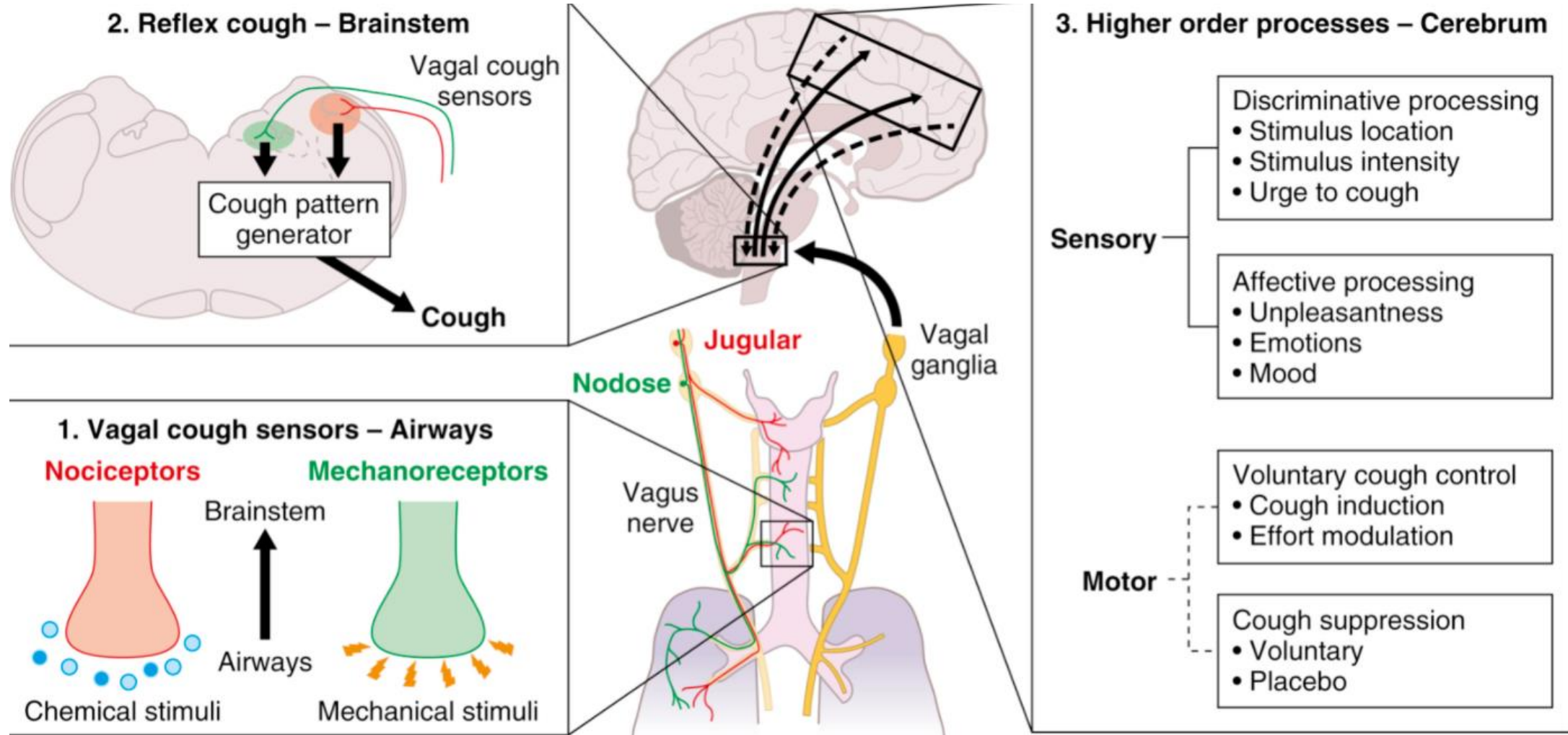
- Cough hypersensitivity syndrome **as a diagnosis**



# Cough hypersensitivity syndrome

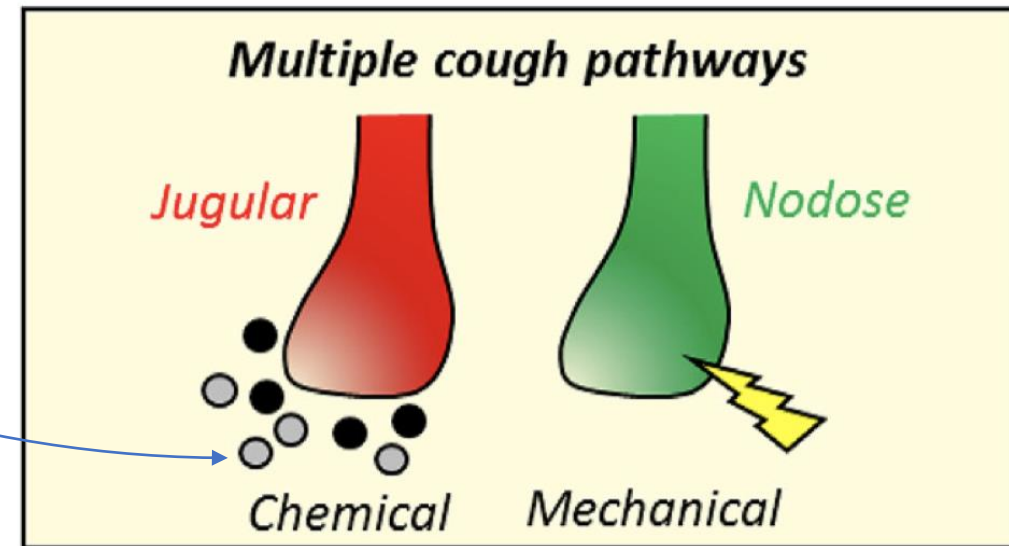
- **Sensitive** to inhalation of environmental irritants
  - Perfume, bleach, and cold air
- Sensations of **tickling/irritation** in the **throat**
- **Urge-to-cough**
- ↑ Sensitivity of the neuronal pathway mediating cough
- Unique epidemiology: 2/3 of **female** (peak in **50s-60s**)
  
- Cough hypersensitivity syndrome as a **diagnosis**
  - discourage repetitive tests → **therapeutic trial**

# Physiology of cough reflex



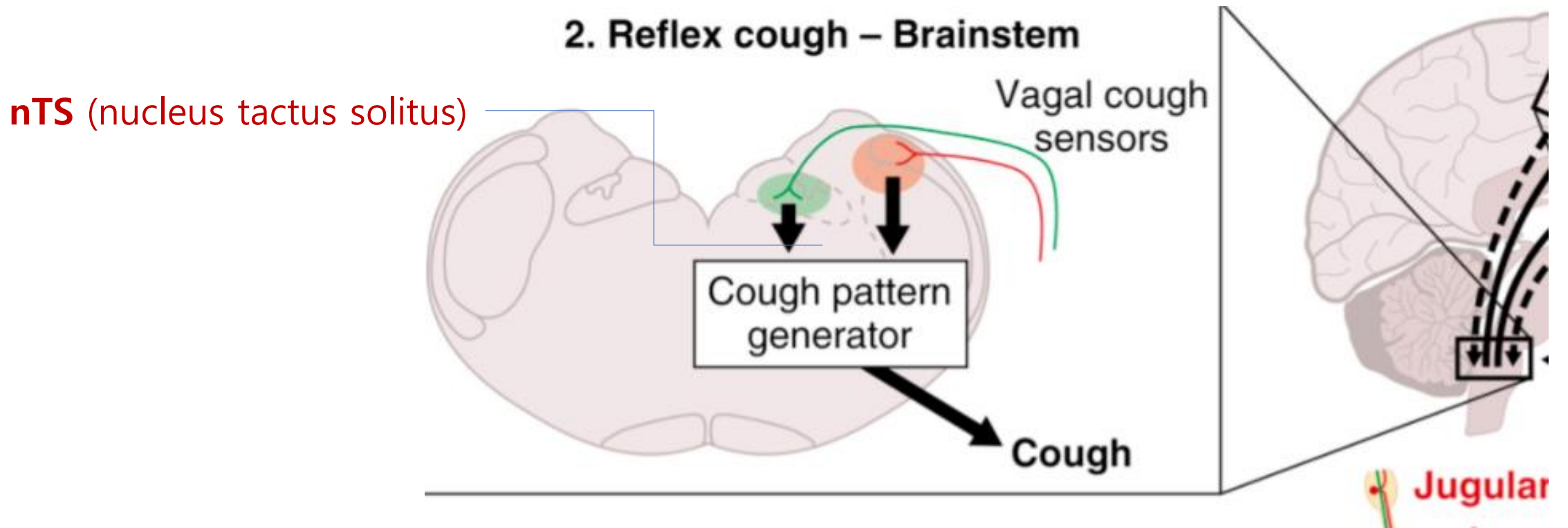
# 1. Vagal cough sensors

- detection in airway: **vagus nerve** terminations
  - **receptors**
  - **ion channels:** TRPV1, TRPA1 TRPV4, ASIC, P2X3
- Jugular neurons
  - **Proximal** (larynx, trachea, main bronchi)
    - Environmental irritants, inflammation
- Nodose neurons
  - **Distal** airways and lung
    - Bronchoconstriction, edema, mucus secretion



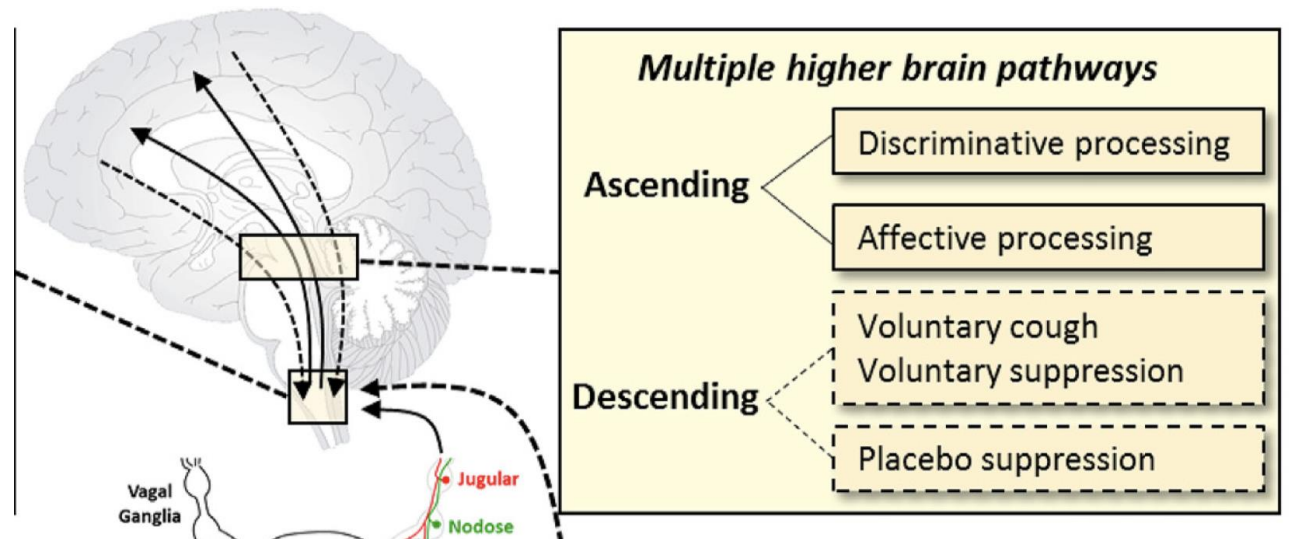
## 2. Cough reflex – brainstem

- vagal axons to brainstem



# 3. Higher brain processing

- **voluntarily cough induction** without peripheral sensory nerve activity
- **modulatory effects** on sensory processing
  - patient conditioning – urge-to-cough evoked by inhaled capsaicin
  - **endogenous opioids**



# Targets for antitussives

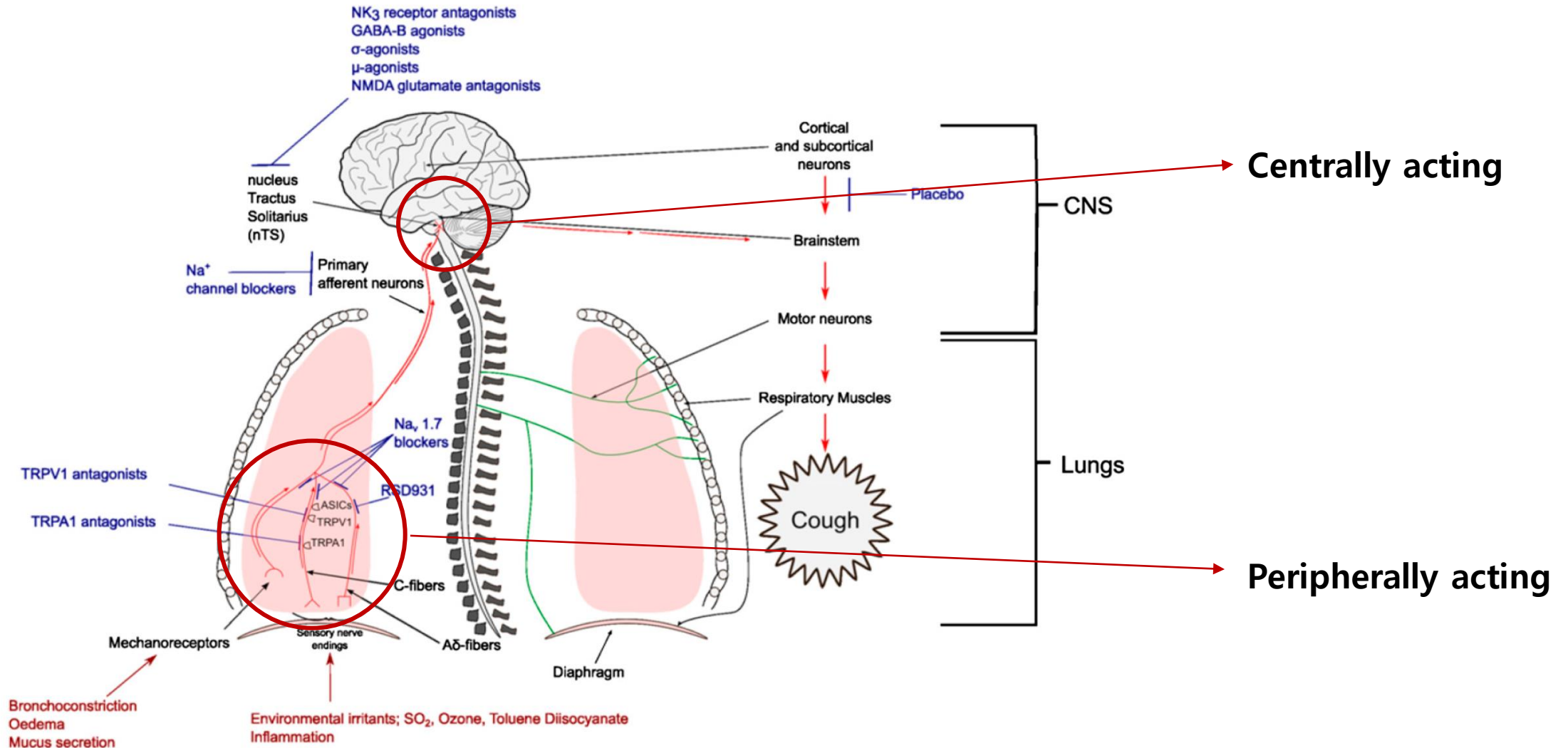


Fig. 2. Multiple vagal afferent nerve subtypes innervate the airways and lungs.

# Cough hypersensitivity syndrome



EUROPEAN RESPIRATORY *journal*

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## ERS guidelines on the diagnosis and treatment of chronic cough in adults and children

Alyn H. Morice, Eva Millqvist, Kristina Bieksiene, Surinder S. Biring, Peter Dicipinigaitis, Christian Domingo Ribas, Michele Hilton Boon, Ahmad Kantar, Kefang Lai, Lorcan McGarvey, David Rigau, Imran Satia, Jacky Smith, Woo-Jung Song, Thomy Tonia, Jan W.K. van den Berg, Mirjam J.G. van Manen, Angela Zacharasiewicz

European Respiratory Journal 2020 55: 1901136; DOI: 10.1183/13993003.01136-2019

## Cough d/t common cold

[ [Evidence-Based Medicine](#) ]



### Pharmacologic and Nonpharmacologic Treatment for Acute Cough Associated With the Common Cold

CHEST Expert Panel Report



Mark A. Malesker, PharmD, FCCP; Priscilla Callahan-Lyon, MD; Belinda Ireland, MD; Richard S. Irwin, MD; Master FCCP; on behalf of the CHEST Expert Cough Panel

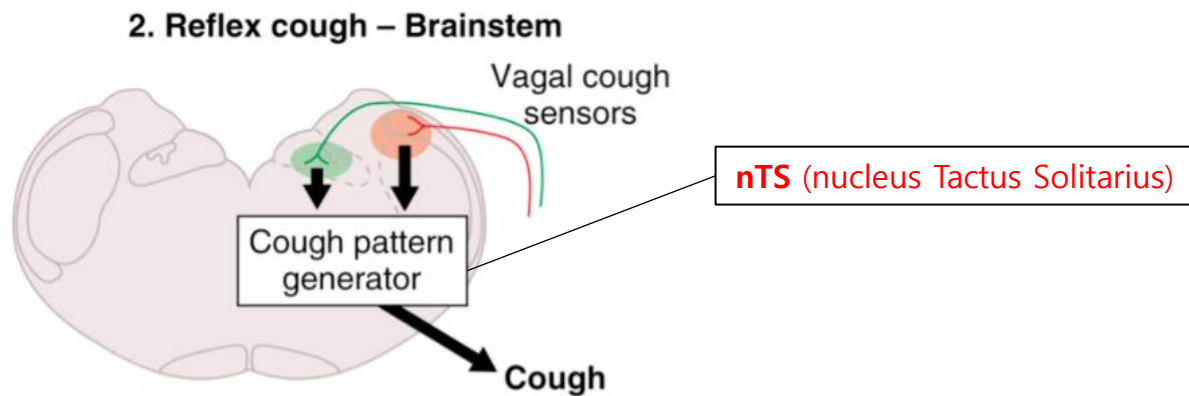
Morice et al. *Eur Respir J* 2020;55:1901136  
Malesker et al. *CHEST* 2017;152:1021

# Agenda

1. Introduction and Physiology of cough
2. Centrally acting antitussive agents
  - dextromethorphan
  - codeine
  - morphine
  - gabapentin and pregabalin
3. Peripherally acting antitussive agents

# Dextromethorphan

- first reported in 1953
- mc **non-opioid central antitussive**
  - no undesirable side effects of codeine
    - drowsiness, nausea, dependency, and constipation
  - Unclear mechanism
    - antagonize NMDA glutamate receptors in nTS



# Dextromethorphan

- active ingredients in many OTC medicines
  - 일반 의약품 성분(약 200개)

## 약품상세검색














Medicines detail search

통합검색 **제품** Q&A 건강뉴스 의학뉴스 블로그 카페 전문정보 웹문서 북약지도

검색결과: 총 209개 중 1 - 20

유통중인 제품

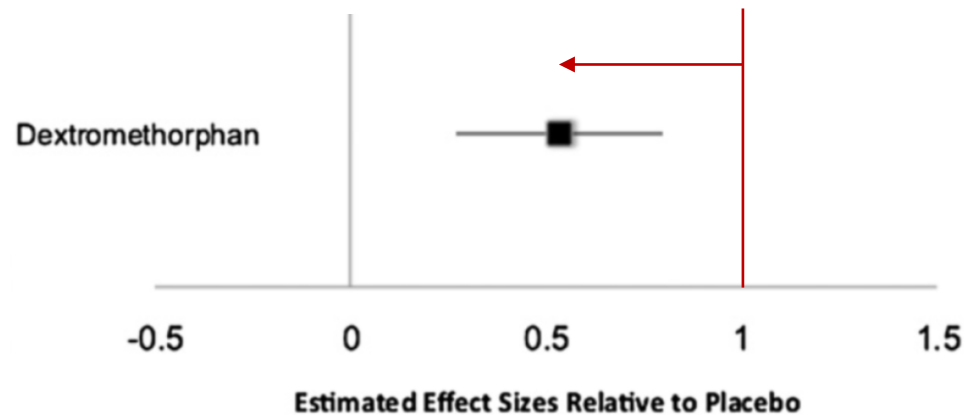
[유통정보가 확인되지 않았](#)

제품 정보 미리보기:						
제품명 ▲	임부	보험코드	판매사	성분/함량	구분	보험
 가기코프캡슐		645204540	 에이프로젠제약(주)	Noscapine 10mg 외 4개	일반	비급여
 감콜캡슐		622800150	 (주)마더스제약	Chlorpheniramine Maleate 1MG 외 8개	일반	비급여
 게보콜캡슐		000000000	 삼진제약(주)	Ibuprofen 50mg 외 6개	일반	비급여
 고프레넥스연질캡슐		643703490	 국제약품(주)	Guaifenesin 100mg 외 3개	일반	비급여
 그날엔코프에스연질캡슐		648103360	 경동제약(주)	Trimetoquinol hydrochloride hydrate 1mg 외 4개	일반	비급여
 그날엔콜드연질캡슐		648103150	 경동제약(주)	Pseudoephedrine hydrochloride 15mg 외 4개	일반	비급여

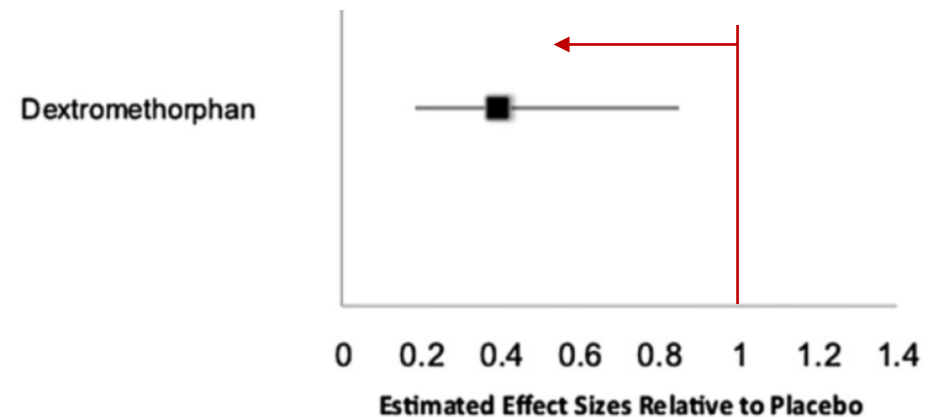
# Dextromethorphan

- Meta-analysis (vs. Placebo)

Cough **severity** (5 studies)



Cough **frequency** (2 studies)

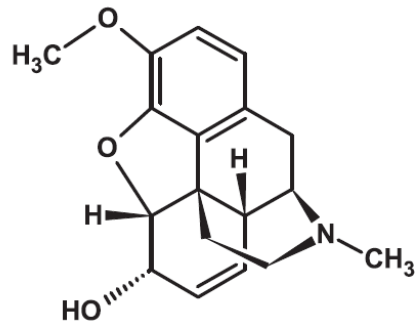


- Limitations

- 분석 연구 대상 환자군의 기침원인, 치료방법, 평가 방법이 일정하지 않음

# Codeine

- traditional **opiate** used for cough
  - central antitussive activity
  - prodrug
    - **Liver cytochrome P450** → morphine: major therapeutic action
    - **CYP2D6**: genetic variability in drug metabolism
- Carefully use in patients with **liver dysfunction**
  - caution in concurrent use with **dextromethorphan**  
(two agents compete for metabolism)



# Codeine

## • 국내 전문 의약품 5개 유통

▶ 의약품명 (유통중인 제품) 5개

제품명	임부	보험코드	판매사	성분/함량	구분	보험	약가	바로가기	제품정보
구주인산코데인정	D	669800390	 구주제약(주)	Codeine phosphate 20mg	전문	급여	95원	 	<a href="#">▶ 수정요청</a>
디코데서방정(주석산수소디히드로코데인)	B	657800350	 하나제약(주)	Dihydrocodeine Tartrate 60mg	전문	급여	472원	 	<a href="#">▶ 수정요청</a>
명문인산코데인정(코데인인산염수화물)	D	649801470	 명문제약(주)	Codeine phosphate 20mg	전문	급여	95원	 	<a href="#">▶ 수정요청</a>
비씨인산코데인정	D	653100790	 (주)비씨월드 제약	Codeine phosphate 20mg	전문	급여	95원	 	<a href="#">▶ 수정요청</a>
하나인산코데인정	D	657802830	 하나제약(주)	Codeine phosphate 20mg	전문	급여	95원	 	<a href="#">▶ 수정요청</a>



### 코O 시럽



In 100 ml:  
 - Dihydrocodeine 50 mg  
 - **Chlorpheniramine** maleate 15 mg  
 - **Methylephedrine** HCl 131.25 mg  
 - Ammonium Cl 1 mg

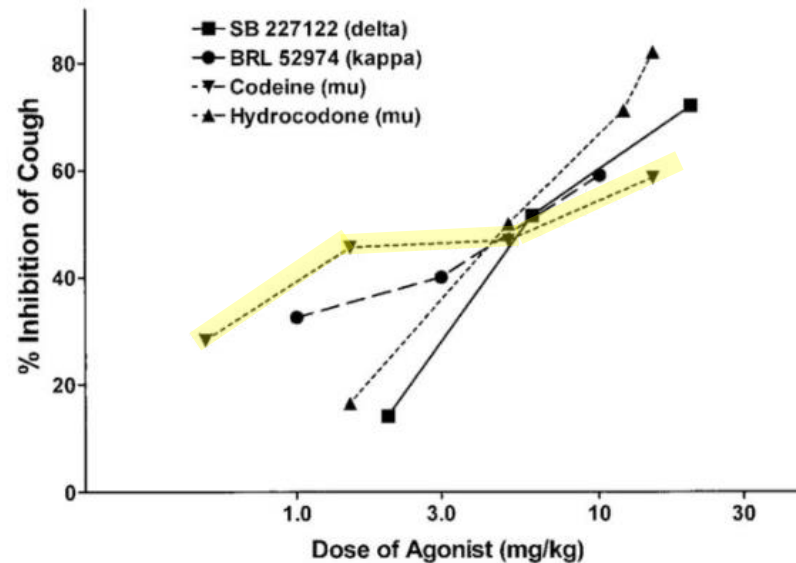
### 코OO 시럽



In 100 ml:  
 - Dihydrocodeine 50 mg  
 - **Chlorpheniramine** maleate 15 mg  
 - **Methylephedrine** HCl 131.25 mg  
 - Guaifenesin 375 mg

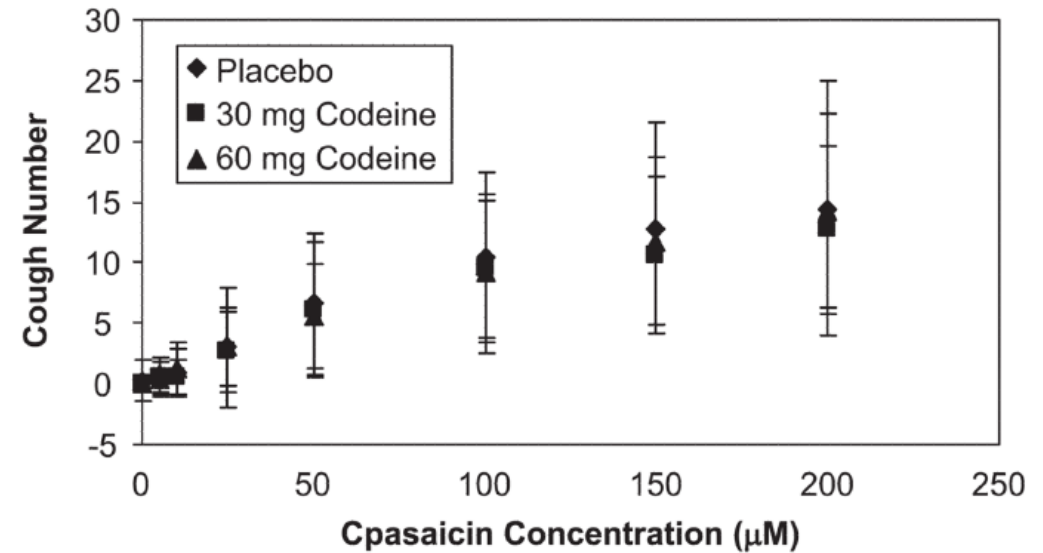
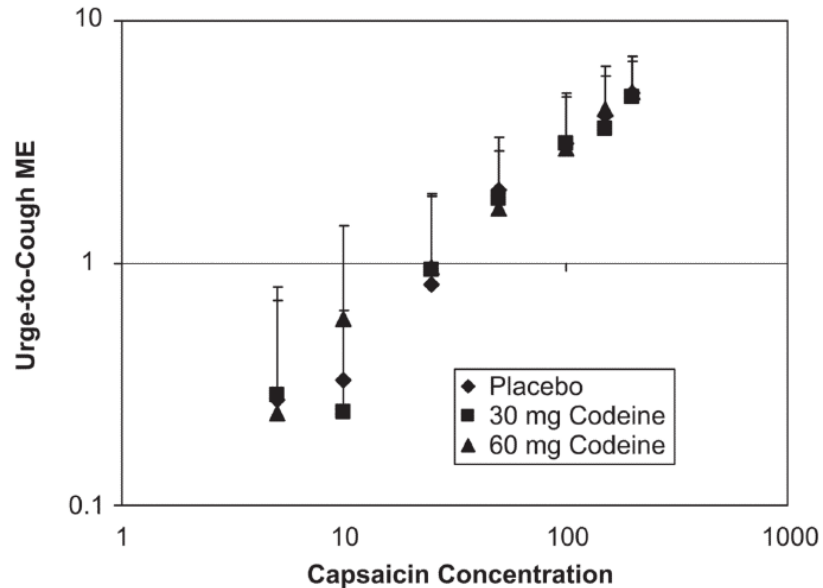
# Codeine

- Animal study
  - conscious guinea pigs
  - codeine → greater than 60% antitussive therapy
  - Opioid receptors mediate inhibition of cough



# Codeine

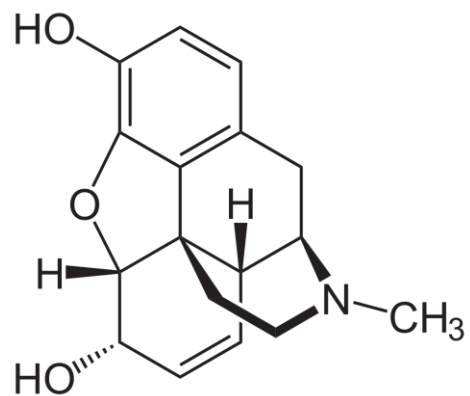
- Cough evoked by capsaicin
- Outcomes: **urge-to-cough sense** and **cough number**



Placebo vs. 30 mg codeine vs. 60 mg codeine: **no intergroup difference**

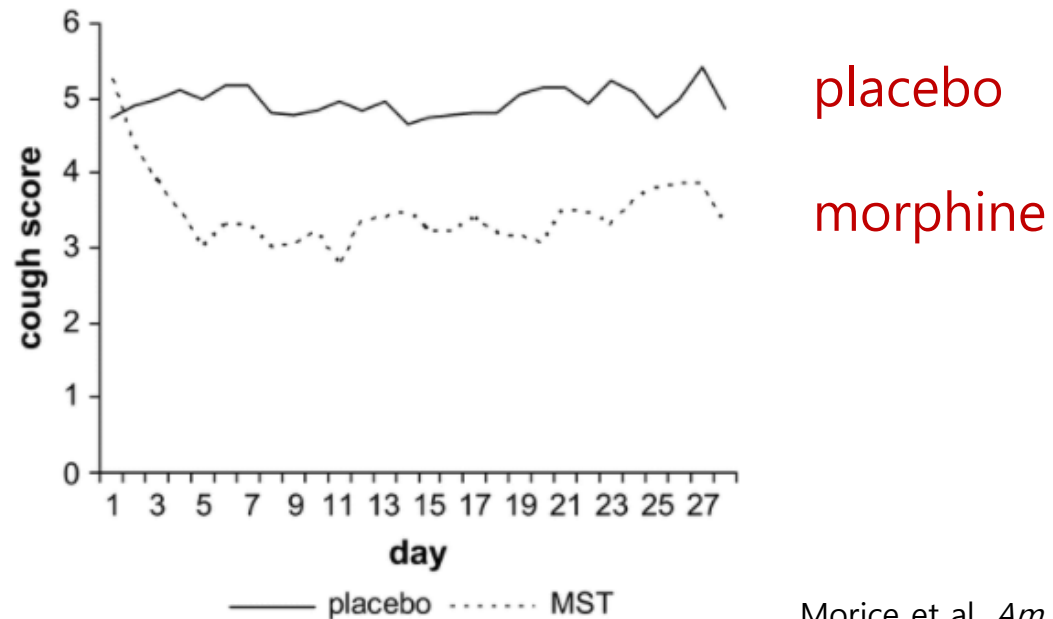
# Morphine

- long history of use
- particularly in the **palliative care** setting
  - **chronic cough** research → metabolites of codeine



# Morphine

- Randomized double-blind placebo-controlled study
  - Crossover design
  - Patients with **chronic cough**
    - 5 mg of morphine twice daily for 1 month vs. Placebo (n = 27)
    - 10 mg of morphine twice daily for 1 month vs. Placebo (n = 18)



# Morphine



ERS guidelines on the diagnosis and treatment of chronic cough in adults and children

- Chronic refractory cough
  - Low-dose morphine (5–10 mg twice daily)
  - Strong recommendation/Moderate level of evidence
  - ½ of patients responded to opiates
  - stop if there is no response in 1 or 2 weeks

# Morphine

- Limitations for using in chronic cough
  - legal issues
  - ceiling effect of therapeutic responses: ~20mg of daily dose
- **None of opiates:** viewed as the gold standard
  - marked individual variance in response
  - morphine may be more reliable than codeine

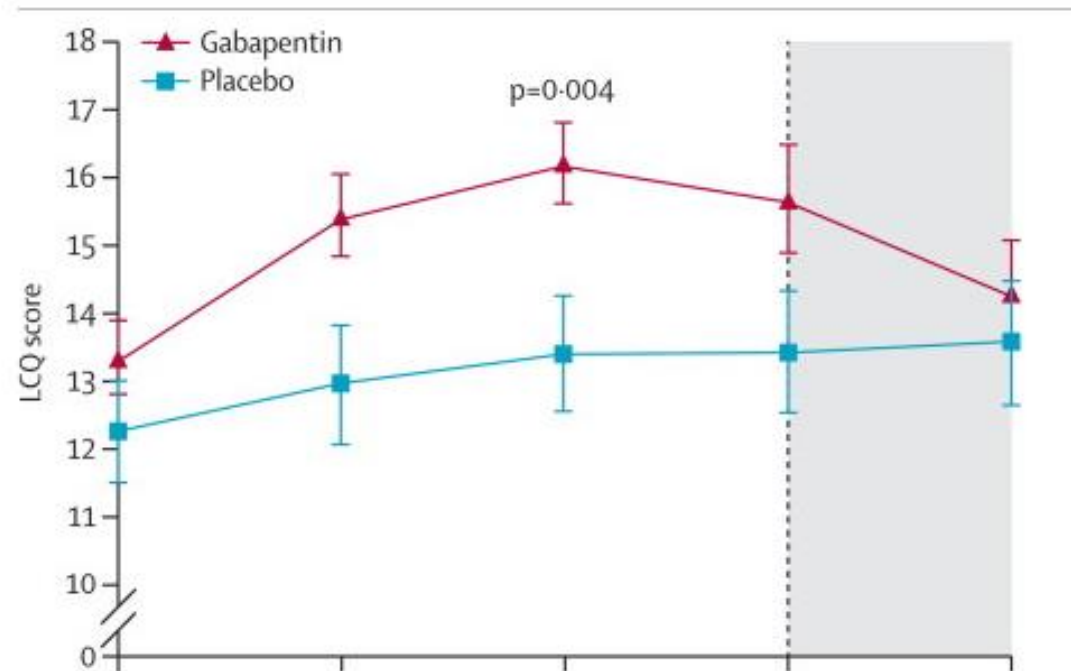
# Gabapentin and pregabalin

- reduce chronic neuropathic pain via central mechanism
  - voltage-gated calcium channel blocker
  - inhibit neurotransmitter release
  
- **Central mechanism** → effective in chronic cough?

# Gabapentin

- RCT
  - 62 patients with refractory chronic cough
  - Gabapentin (~1800 mg/day) vs. Placebo
  - 10 weeks duration

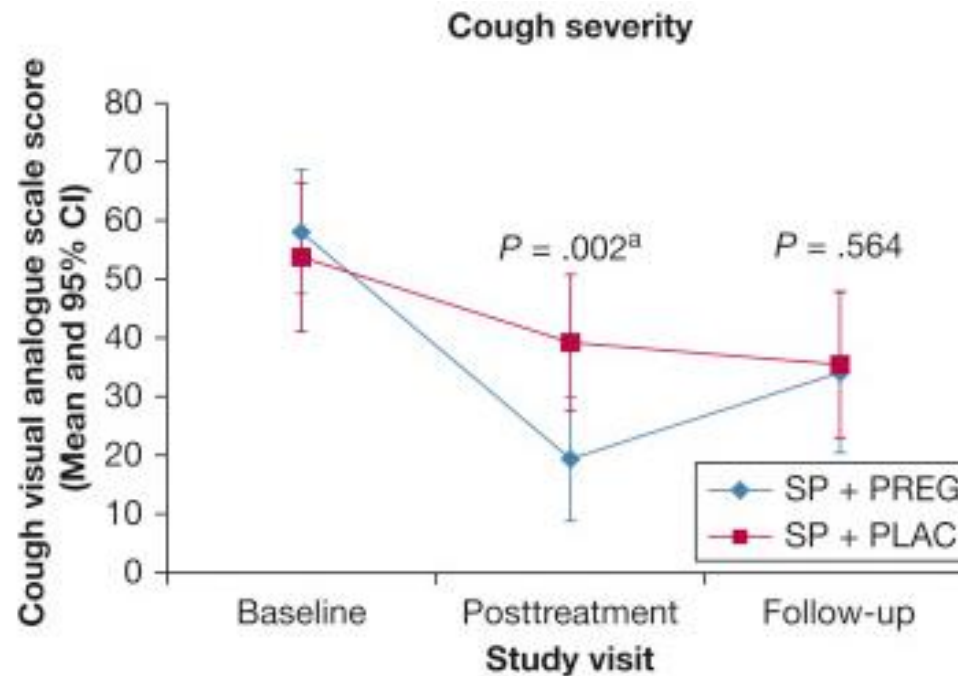
Cough-related  
QoL score



# Pregabalin

- RCT
  - 40 patients with refractory chronic cough
  - Pregabalin with SPT vs. Placebo with SPT
    - SPT = speech pathology treatment
  - 14 weeks

Cough VAS



# Gabapentin and pregabalin



ERS guidelines on the diagnosis and treatment of chronic cough in adults and children

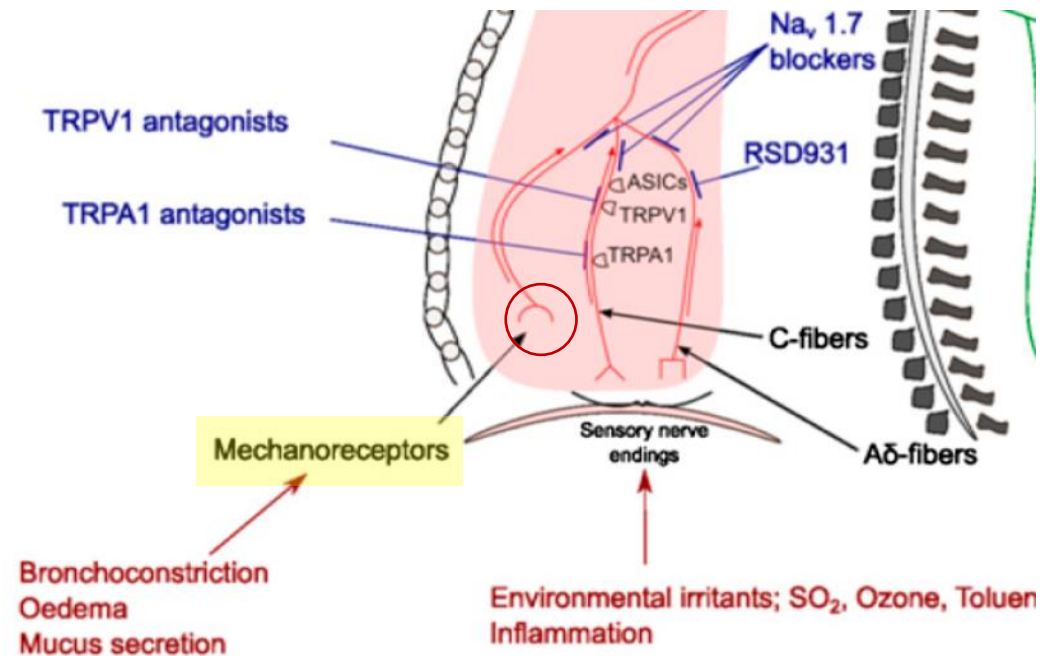
- Chronic refractory cough
  - Conditional recommendation/Low level of evidence
  - S/E: blurred vision, disorientation, dizziness, dry mouth, and nausea
    - low dosage (300 mg once a day) → gradual increase
    - up to 1800 mg/day (gabapentin)

# Agenda

1. Introduction and Physiology of cough
2. Centrally acting antitussive agents
3. Peripherally acting antitussive agents
  - benzonatate
  - levodropropizine
  - theobromine
  - antihistamine
  - novel drug

# Benzonatate

- used since 1958
- **anesthetizing stretch receptors** in lung and pleura



# Benzonatate

- Case reports of using for opioid-resistant cough
  - advanced cancer
- fatal overdoses were reported (< 10 years old)
  - tremors, convulsion, coma, cardiac arrest
- 국내 전문 의약품 1개 유통

약품상세검색  
Medicines detail search

약품상세검색

통합검색 제품 Q&A 건강뉴스 의약뉴스 블로그 카페 전문정보 웹문서 복약지도 심사지침 효능효과

성분 1개 중 1-1

영문 성분명	한글 성분명	제품 리스트
Benzonatate	벤조나테이트	조회

유통중인 제품 1개 중 1-1

제품명	임부	보험코드	판매사	성분/함량	구분	보험	약가	조회수	대체	수정
지롤연질캡슐(벤조나테이트)		643200970	동성제약(주)	Benzonatate 100mg	전문	급여	72원	유료	조회	요청

# Benzonatate + Guaifenesin

- RCT
  - Guaifenesin: FDA-approved expectorant
  - cough d/t acute viral infections (n = 30)
  - Benzonatate vs. Guaifenesin vs. Combination vs. placebo
  - 3 separate days within 7 day period (double-blind fashion)
- cough reflex sensitivity ↓
  - **Guaifenesin + Benzonatate** vs. Placebo (p < 0.001)




# Guaiifenesin

- active ingredients in many OTC medicines
  - 일반 의약품 성분(약 200개)

통합검색 **제품** Q&A 건강뉴스 의약품스 블로그 카페 전문정보 웹문서 복약

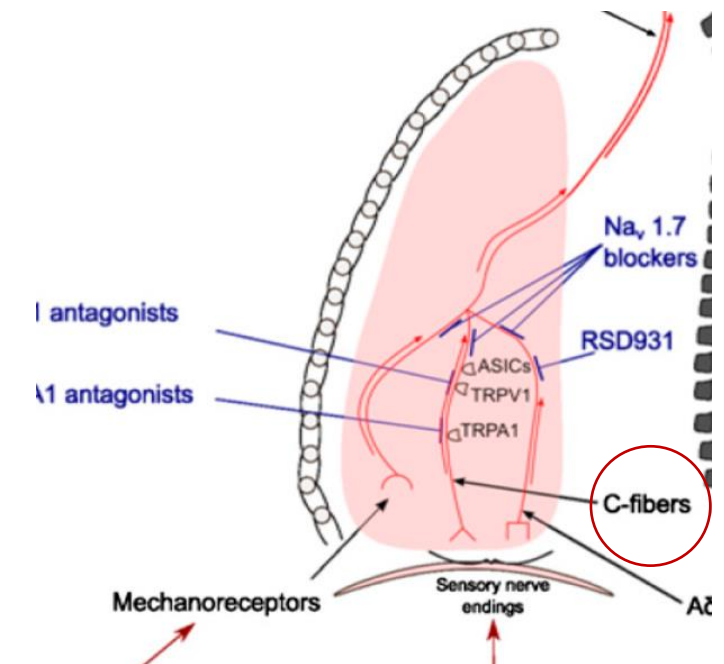
검색결과: 총 212개 중 1 - 20

유통중인 제품 [유통정보가 확인](#)

제품 정보 미					
제품명 ▲	임부	보험코드	판매사	성분/함량	구분
 게보콜캡셀	C	000000000	 삼진제약(주)	Ibuprofen 50mg 외 6개	일반
 고프레넥스연질캡슐		643703490	 국제약품(주)	<b>Guaiifenesin</b> 100mg 외 3개	일반
 그날엔코프에스연질캡슐		648103360	 경동제약(주)	Trimetoquinol hydrochloride hydrate 1mg 외 4개	일반
 그날엔콜드연질캡슐		648103150	 경동제약(주)	Pseudoephedrine hydrochloride 15mg 외 4개	일반
 그날엔콜드플러스연질캡슐		648103950	 경동제약(주)	Pseudoephedrine hydrochloride 15mg 외 4개	일반
 그린롤샷에스캡슐		643600190	 (주)녹십자	Pseudoephedrine hydrochloride 15mg 외 6개	일반

# Levodropropizine

- influence firing of **sensory C-fibers**
- short-term symptomatic treatment
  - adults
  - children older than 2 years
- peak plasma levels within 40–60 minutes
  - rapid GI absorption
  - not need to be adjusted in elderly



# Levodropropizine

- patients with allergic asthma or chronic bronchitis
  - reduced cough vs. Placebo
- patients with acute and chronic bronchitis
  - reduced cough severity/frequency
  - dose-dependent manner















# Levodropropizine

- 전문 의약품으로 유통(약 140개)

통합검색 **제품** Q&A 건강뉴스 의약뉴스 블로그 카페 전문정보 웹문서 복약지도

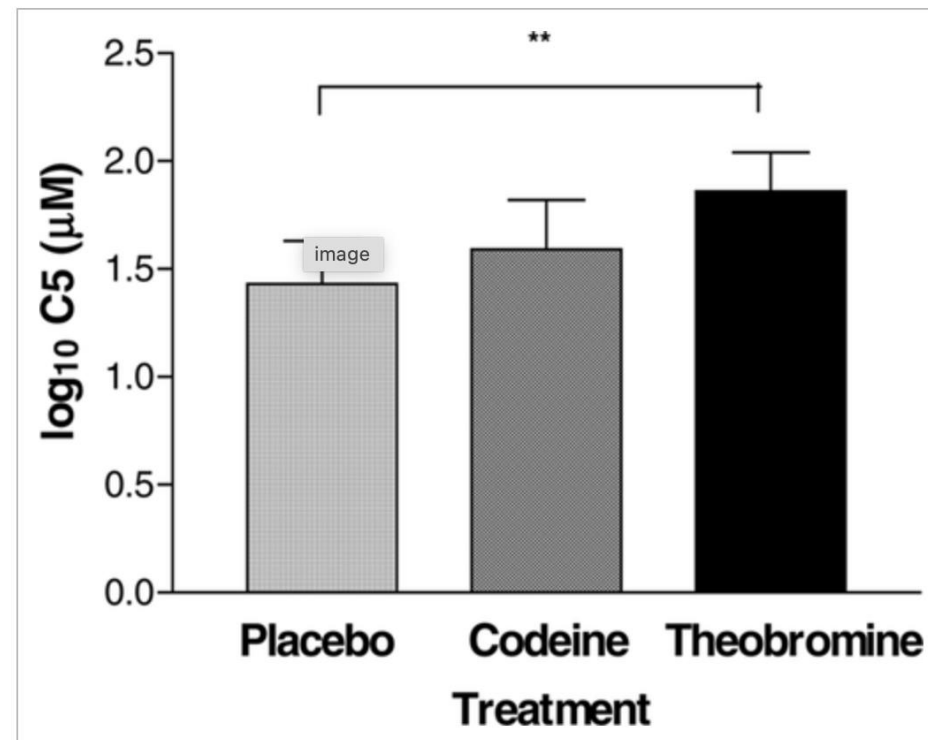
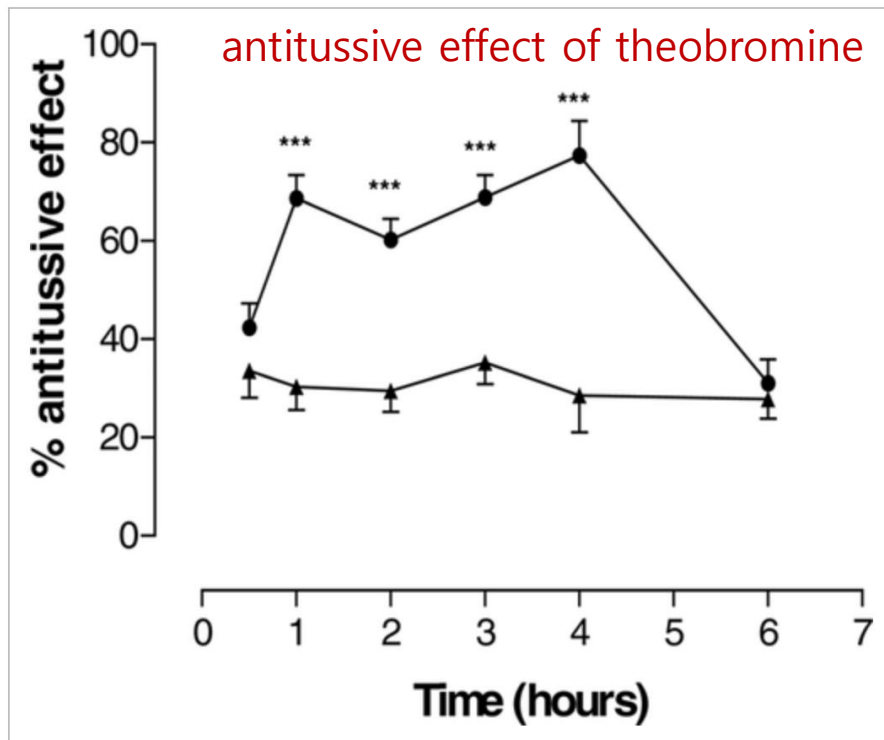
검색결과: 총 146개 중 1 - 20

유통중인 제품 [> 유통정보가 확인되지 않음](#)

제품 정보 미리보기:						
제품명 ▲	임부	보험코드	판매사	성분/함량	구분	보험
 건일레보드로프로피진시럽 500mL		646802881	 건일제약(주)	Levodropropizine 600mg	전문	급여
 건일레보드로프로피진정		646802870	 건일제약(주)	Levodropropizine 60mg	전문	급여
 글로피진정(레보드로프로피진)		693200700	 (주)한국글로벌제약	Levodropropizine 60mg	전문	급여
 네오투스서방정(레보드로프로피진)		644103040	 제이더블유신약(주)	Levodropropizine 90mg	전문	급여
 네오투스정(레보드로프로피진)		644102490	 제이더블유신약(주)	Levodropropizine 60mg	전문	급여
 독립레보드로프로피진정		057700020	 독립바이오제약(주)	Levodropropizine 60mg	전문	급여
 드로니즈시럽(레보드로프로피진)(500mL)		670402001	 (주)휴온스메디케어	Levodropropizine 600mg	전문	급여

# Theobromine

- TRPV-1 차단 → Vagus nerve 활성화 억제
- Guinea pigs (citric acid) and human subjects (capsaicin)



# Theobromine

- 전문 의약품으로 유통(약 32개)



통합검색   **제품**   Q&A   건강뉴스   의약뉴스   블로그   카페   전문정보   웹문서   복약지도   심사지침

검색결과: 총 36개 중 1 - 20

**유통중인 제품** [▶ 유통정보가 확인되지 않았거나](#)

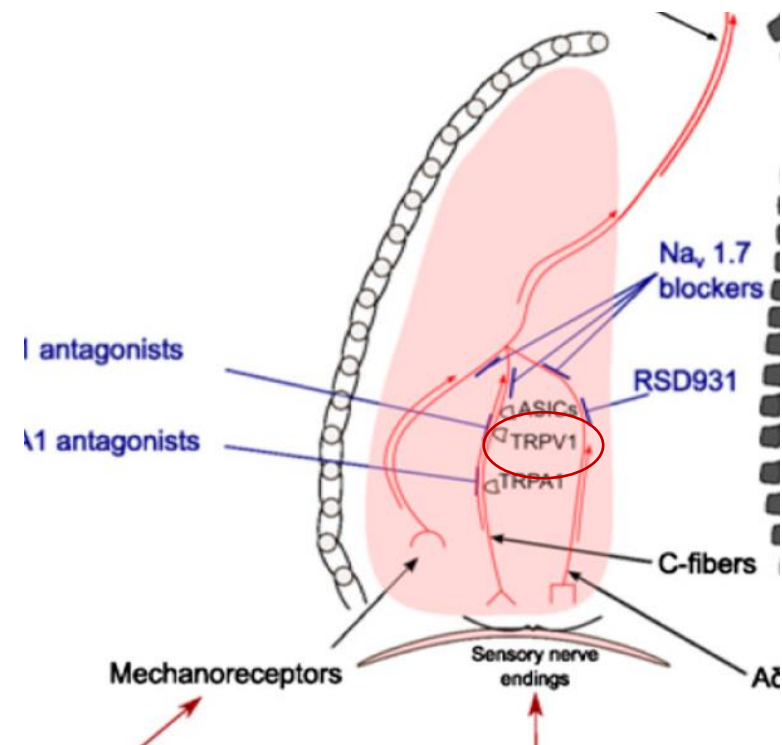
제품명 ▲	임부	보험코드	판매사	성분/함량	구분	보험	약가	제품 정보 미리보기: <
 글로코프캡슐300mg(테오브로민)		693201970	 (주)한국글로벌제약	Theobromine 300mg	전문	급여	102원	
 넥스코프캡슐(테오브로민)		662503840	 (주)넥스팜코리아	Theobromine 300mg	전문	급여	102원	
 뉴코프캡슐300mg(테오브로민)		053600510	안국뉴팜(주)	Theobromine 300mg	전문	급여	102원	
 대우브로민캡슐300mg(테오브로민)		649605340	 대우제약(주)	Theobromine 300mg	전문	급여	102원	
 브로코프캡슐300mg(테오브로민)		646004370	 (주)메디카코리아	Theobromine 300mg	전문	급여	102원	
 삼성테오브로민캡슐300mg		642307060	 삼성제약(주)	Theobromine 300mg	전문	급여	102원	
 애니로민캡슐300mg(테오브로민)		651205060	 삼천당제약(주)	Theobromine 300mg	전문	급여	102원	

# H<sub>1</sub>-Receptor antagonists

- numerous animal studies – antitussive
- unclear mechanism
  - **anticholinergic** (sedative) effects?
  - antagonize **stretch receptors**?
- independent of “sedative effects” and “effects on minute ventilation”

# H<sub>1</sub>-Receptor antagonists

- First-generation antihistamine dexbrompheniramine
- **inhibit TRPV<sub>1</sub> activation**
  - potential mechanism
  - rat experiment study



# H<sub>1</sub>-Receptor antagonists

## 코O 시럽



In 100 ml:

- Dihydrocodeine 50 mg
- **Chlorpheniramine** maleate 15 mg
- **Methylephedrine** HCl 131.25 mg
- Ammonium Cl 1 mg

## 코OO 시럽



In 100 ml:

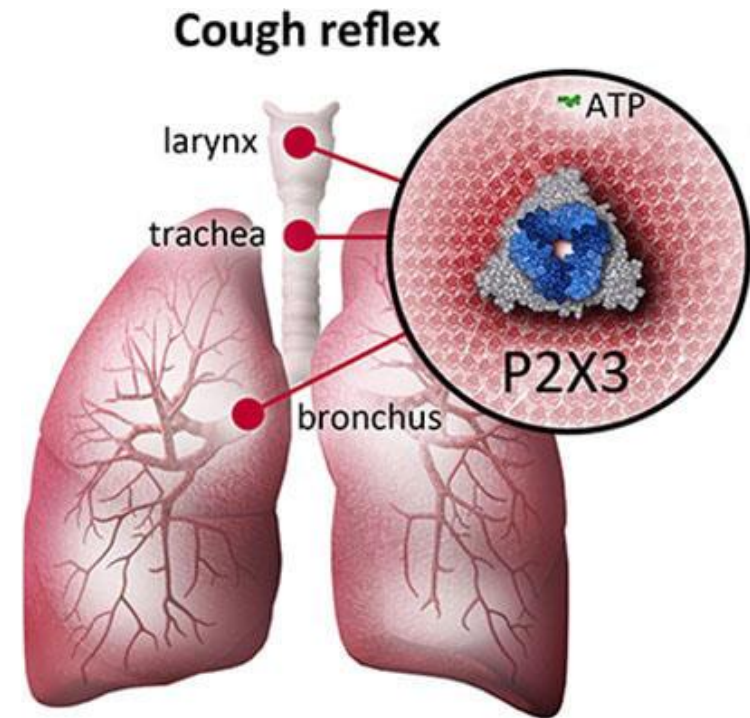
- Dihydrocodeine 50 mg
- **Chlorpheniramine** maleate 15 mg
- **Methylephedrine** HCl 131.25 mg
- Guaifenesin 375 mg

# H<sub>1</sub>-Receptor antagonists

- First generation antihistamine + Decongestants
  - Chronic cough d/t upper airway cough syndrome
  - Acute cough d/t common cold
- Limitations of recommendation
  - Largely based on clinical experience and expert opinions
  - Lack of adequately powered RCT

# P2X3 receptor antagonist - Gefapixant

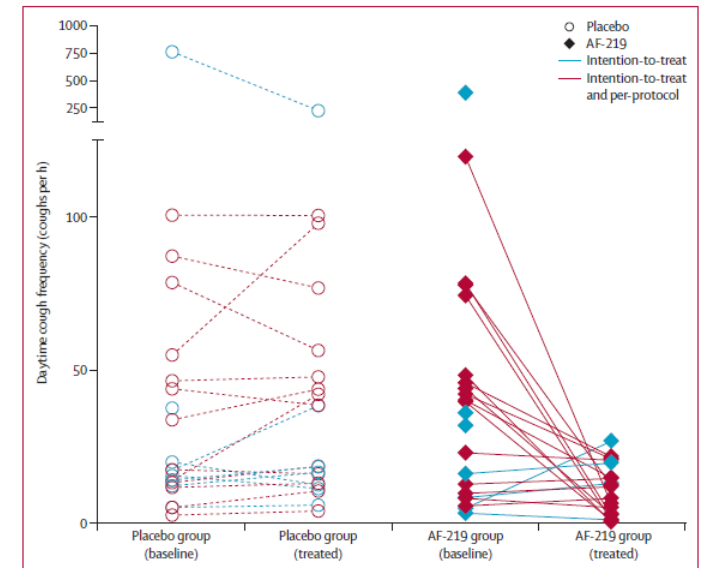
- **ATP-gated ion channel**
  - peripheral sensory nerves in airways
- P2X3 receptor antagonist
  - Novel drug for chronic refractory cough?



# Proof-of-concept study

- 34 individuals with chronic refractory cough
  - RCT (AF-219 vs. placebo)
  - Outcomes
    - Daytime cough frequency (primary endpoint): baseline and 2 week
    - **75% reduced (p = 0.0003)**

	AF-219		Placebo		Difference at 2 weeks	
	Baseline	Week 2	Baseline	Week 2	Placebo-adjusted effect of AF-219 (95% CI)*	p value
<b>Daytime cough frequency</b>						
<b>ITT population</b>						
Patients in analysis	19	19	21	21	..	..
Coughs per h	37.09 (32-23)	10.97 (8-30)	65.45 (163-36)	43.59 (51-42)	-75% (-88 to -50)	0.0003
<b>PP population</b>						
Patients in analysis	14	14	14	14	..	..
Coughs per h	45.15 (33-23)	10.51 (7-47)	37.30 (32-39)	41.57 (31-78)	-84% (-94 to -60)	0.0005



# Phase 2 study

- Chronic refractory cough (n = 253)
  - Placebo or Gefapixant (7.5mg, 20mg, or 50mg)
  - 84 days
  - Outcome: placebo-adjusted change from baseline in awake cough frequency

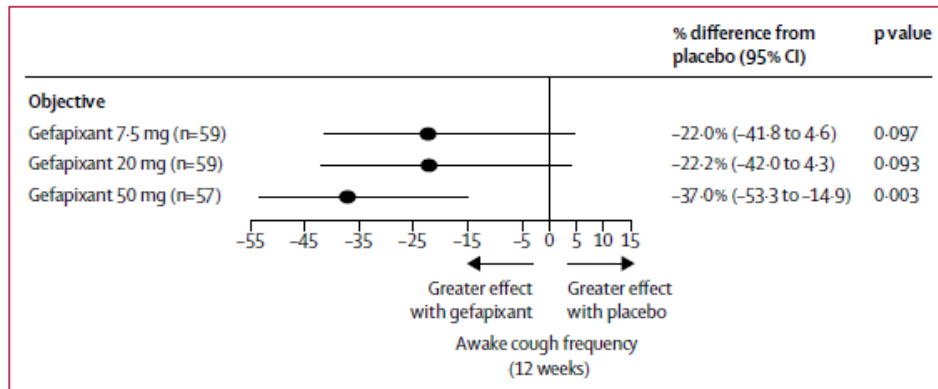
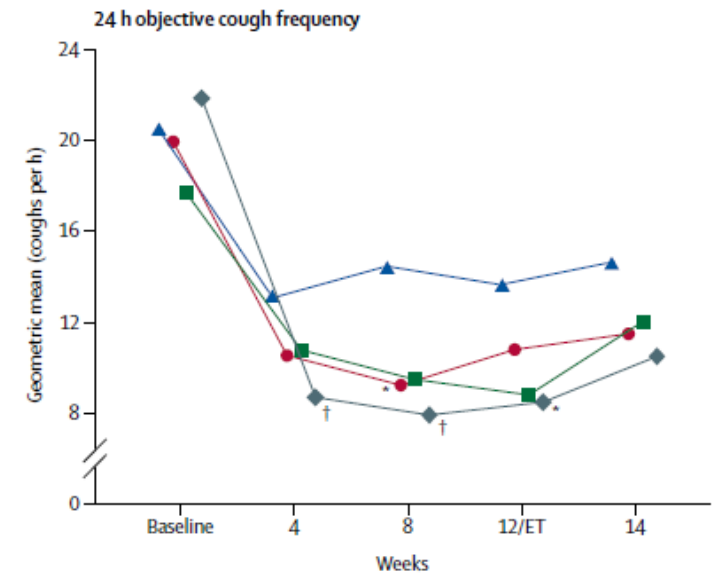
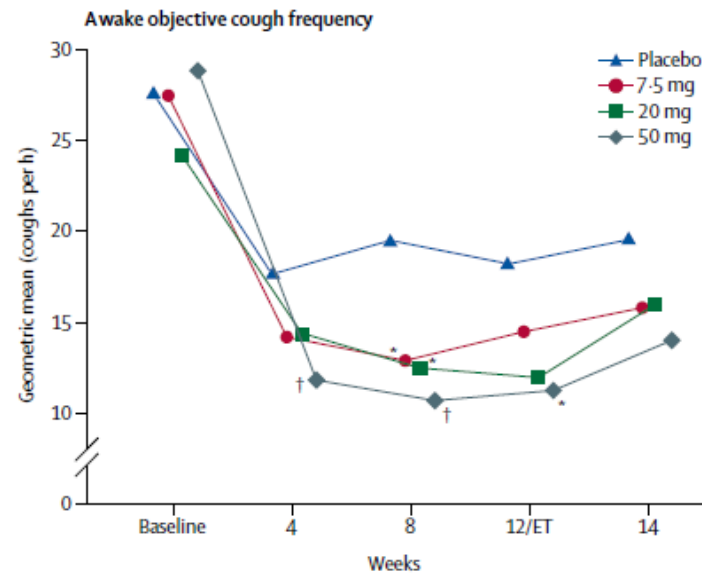


Figure 2: Forest plot of change in awake cough frequency with gefapixant versus placebo in the full analysis set

Data were assessed using a mixed model repeated measures analysis that included fixed effects for treatment group, visit, country, and treatment-by-visit interaction, and the baseline value as a covariate. The analysis of change from baseline in awake objective cough frequency and 24-hour objective cough frequency was based on log-transformed data.



# Phase 3 study

## A Study of Gefapixant (MK-7264) in Adult Participants With Chronic Cough (MK-7264-027)

ClinicalTrials.gov Identifier: NCT03449134

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators.

⚠ Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our [disclaimer](#) for details.

[Recruitment Status](#) ⓘ : Completed  
[First Posted](#) ⓘ : February 28, 2018  
[Results First Posted](#) ⓘ : June 16, 2021  
[Last Update Posted](#) ⓘ : June 16, 2021

### Sponsor:

Merck Sharp & Dohme Corp.

### Information provided by (Responsible Party):

Merck Sharp & Dohme Corp.

- COUGH-1 (n = 730, 12 weeks)
  - 24-hour cough frequency recorded
  - **18.5% reduction** (vs. placebo)
- COUGH-2 (n = 1314, 24 weeks)
  - **14.6% reduction** (vs. placebo)

## FDA accepts gefapixant for review in cough, positioning Merck to get head start on Bayer and Bellus

by Nick Paul Taylor | Mar 1, 2021 8:15am



*FDA is set to make a decision on whether to approve Merck's gefapixant by Dec. 21. (Merck)*

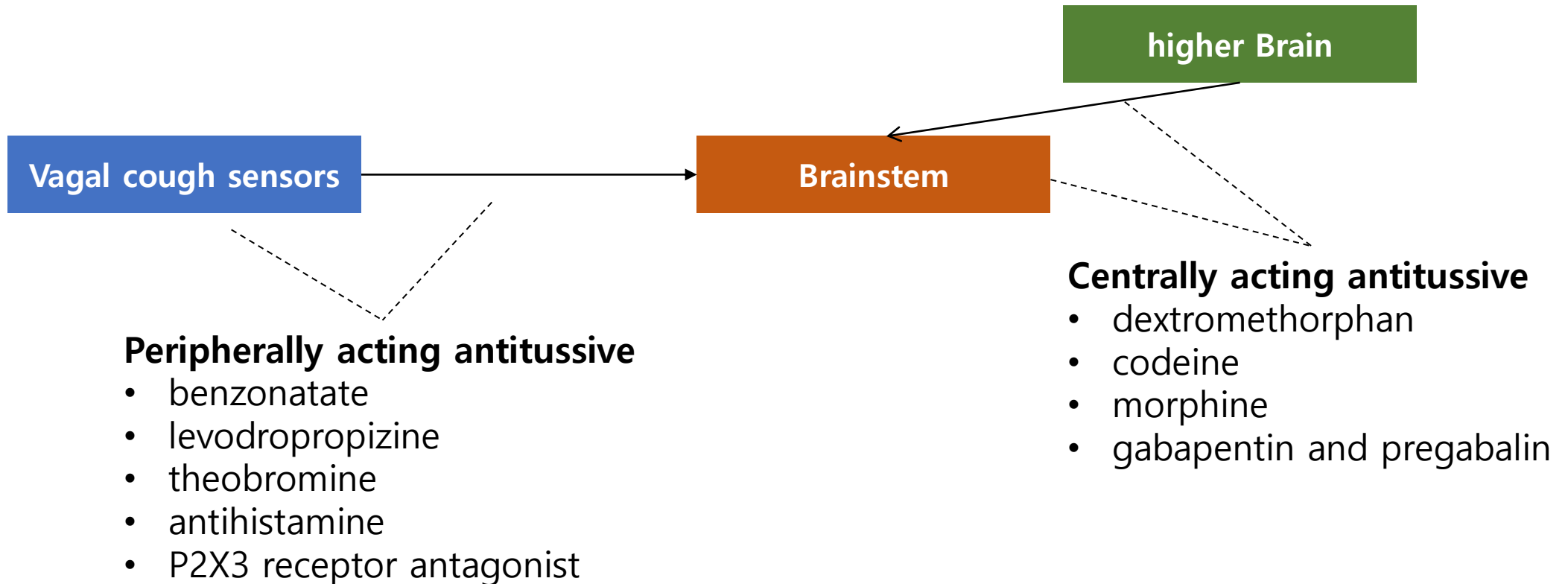


The FDA has **accepted** a filing for approval of Merck's P2X3 receptor antagonist gefapixant for review. Merck is seeking approval on the basis of phase 3 trials that linked the oral drug to improvements in several measures of chronic cough symptoms but confirmed tolerability concerns.

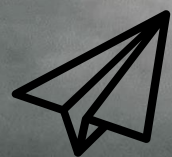
Gefapixant is at the front of a pack of P2X3 prospects in development at companies including Bayer, Bellus Health and Shionogi. Merck validated the target last year in a pair of phase 3 trials, COUGH-1 and COUGH-2, that found gefapixant drove relative risk reduction in 24-hour coughs per hour. Yet, 15% to 20% of subjects on the high dose dropped out due to adverse events.

# Summary

- Physiology of cough and Antitussives



*To the  
End*



**hychoimd@gmail.com**