

CME CAST EPISODE 2

A Guide to New and Emerging Treatment Options for Chronic Cough

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Learning
Objective 1

Evaluate efficacy and safety data for new and emerging treatments for chronic cough.



The Scope of the Problem: Cough

- Cough is the most common reason for primary care visits, with up to 85% receiving prescriptions for treatment.
- Can be acute (< 3 weeks), subacute (3-8 weeks), or chronic (> 8 weeks)
- Prevalence of chronic cough (CC) is estimated at about 10% of adults
 - Estimation difficult due to lack of specific ICD-9/10 code for diagnosis
- CC carries a heavy burden
 - Impaired quality of life; fatigue, affects daily activities like talking, can result in incontinence, and can be perceived as an annoyance by family and co-workers
 - Increased anxiety, frustration, depression, & fear of social gatherings
 - Increased health care utilization and expenditure due to multiple visits to PCP, specialists, testing, multiple prescription & OTC therapy trials, as well as non-pharmacologic therapy.
- Significance of CC is often overlooked by HCP's
- Currently lack acceptably tolerable and efficacious therapies for CC

HCP = health care professional; ICD = International Classification of Disease; OTC = over-the-counter; PCP = primary care provider

1. Visca D, et al. *Eur J Intern Med.* 2020;81:15-21. 2. Weiner M, et al. *Chest.* 2021;159(6):2346-2355. 3. Zeiger, RS, et al. *Perm J.* 2020;24:1-3.
4. Chamberlain SA, et al. *Lung.* 2015;193(3):401-408. 5. Davis D. *Am J Manag Care.* 2020;26(Suppl 11):S246-S250. 6. French CL, et al. *Arch Intern Med.* 1998;158(15):1657-1661.
7. Dicipinigitis PV, et al. *Chest.* 2006;130(6):1839-1843. 8. McGarvey LP, et al. *Cough.* 2006;2:4. 9. Holzinger F, et al. *Dtsch Arztebl Int.* 2014;111(20):356-363.
10. Everett CF, et al. *Cough.* 2007;3:5.

Cough With Identifiable Causes

- Coughs with anatomic etiology
 - i.e. GERD, post-nasal drip, pneumonia, cancer, pulmonary fibrosis
- Appropriate treatment of the cause may resolve the cough
- Pharmacists have a role in:
 - Patient education of possible causes
 - Referral to the appropriate HCP to evaluate and treat
 - Patient counseling of medications prescribed for underlying cause or for cough
- When coughs persist, have we overlooked any possible anatomic cause?

Treating Cough: The Search For An Acceptable Cough Controller

- Last approved cough agent was in 1958
 - dextromethorphan/benzonatate
- Cough drops
- Antihistamines
 - Diphenhydramine
 - Chlorpheniramine (12mg ER tabs better than 4mg short acting)
- Benzonatate
- Dextromethorphan
- Hydrocodone/codeine
 - Extended-release hydrocodone
- Oral corticosteroid bursts

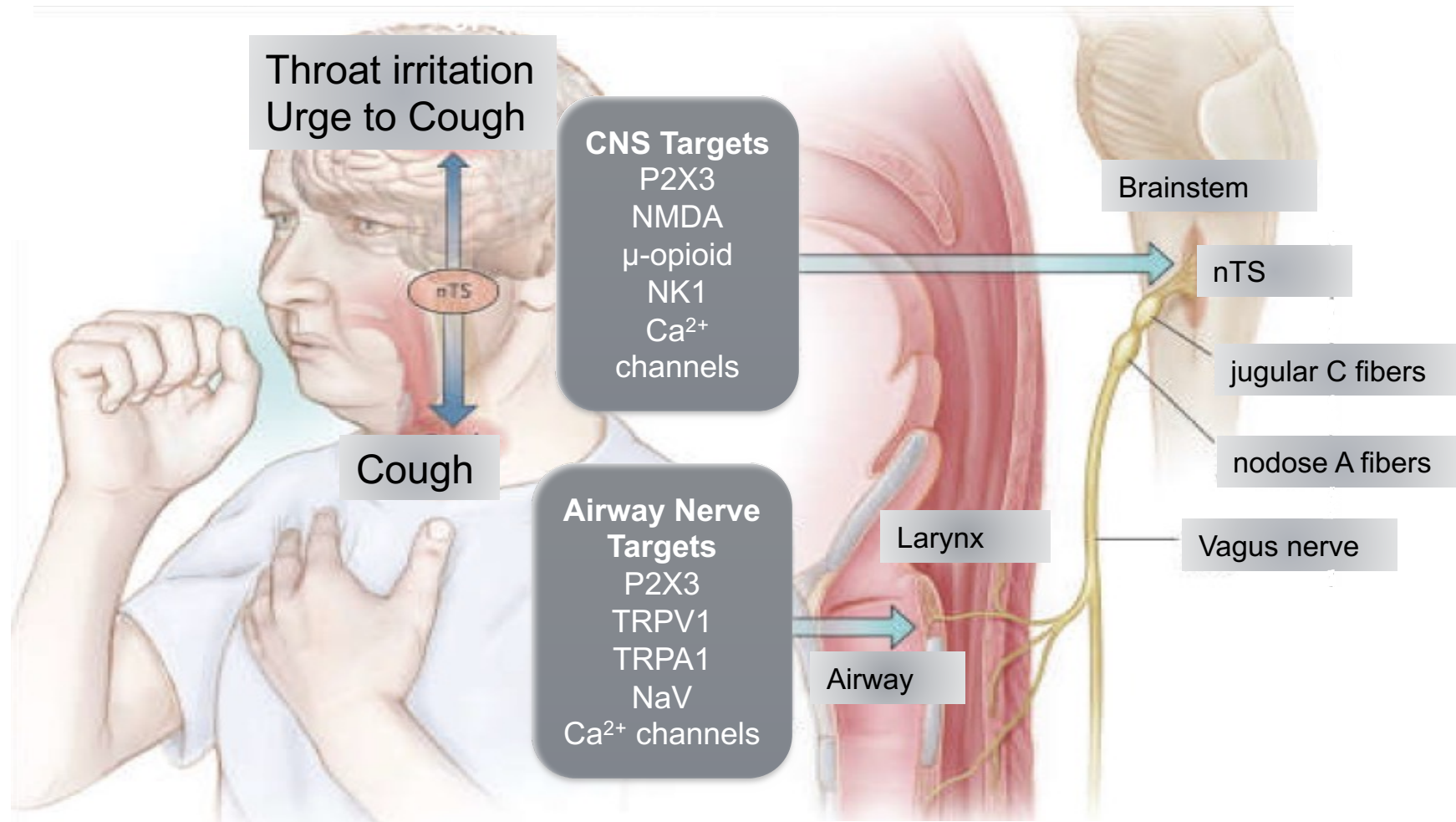
The Cough That Just Does Not Go Away...

- **Chronic Cough:** cough with a duration of > 8 weeks
- **Refractory Chronic Cough (RCC):** a cough that persists despite guideline-based treatment for underlying conditions such as GERD, asthma, and rhinosinusitis
- **Unexplained Chronic Cough (UCC):** a cough that persists longer than 8 weeks, and remains unexplained after investigation

Anatomy Of Cough

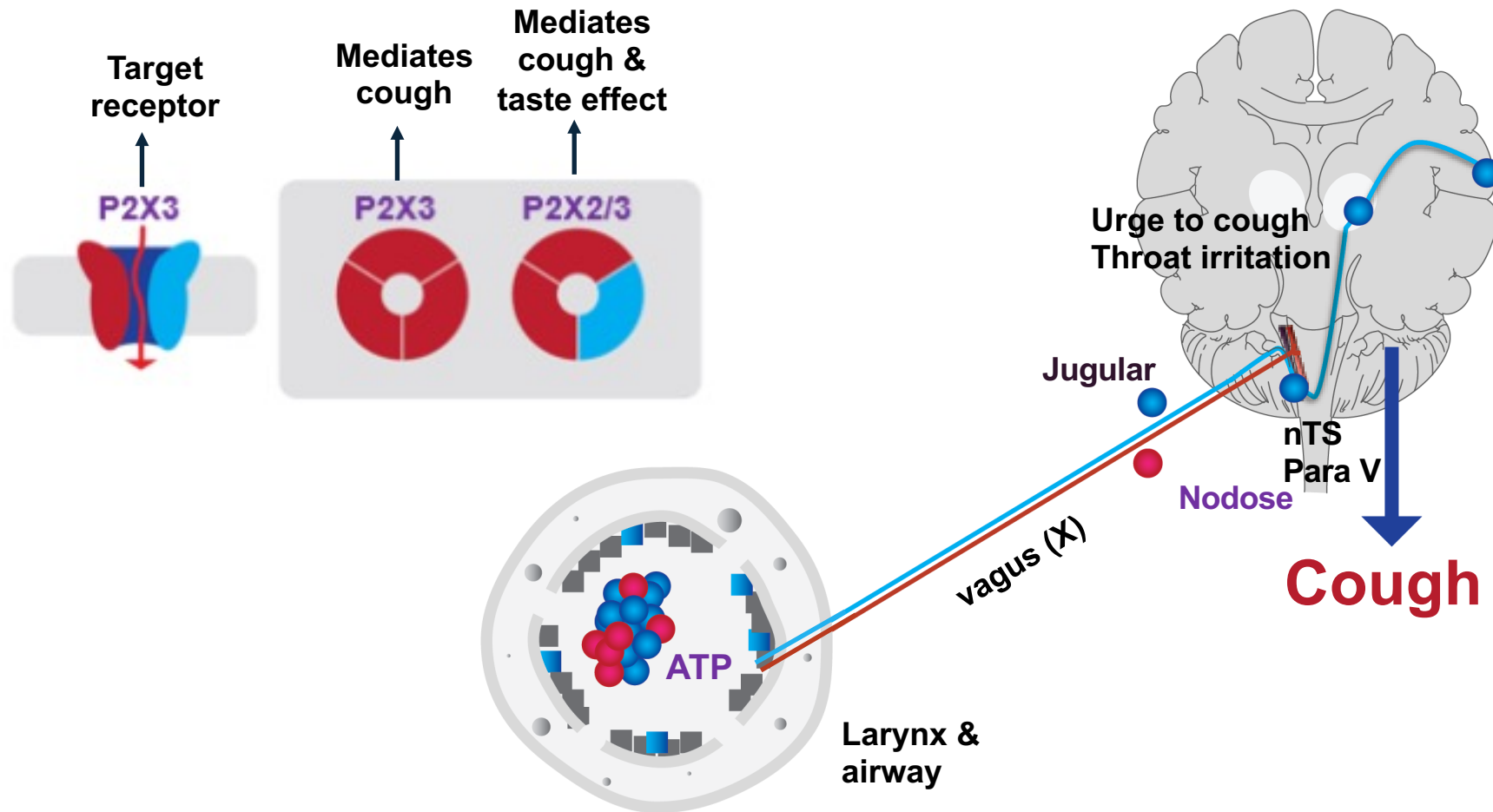
- **Protective cough reflex**
 - “True” cough reflex
 - Protects against aspiration of objects and acid
 - Conscious and anesthetized-difficult to suppress
- **Irritative cough reflex/response**
 - Urge to cough leading to a “cough response”
 - “The tickle in the back of my throat”
 - Chemical irritants and lung inflammation
 - Respiratory virus potent trigger
 - Conscious, but not anesthetized

Pathophysiology of Cough: Targetable Receptors



Ca = calcium; CNS = central nervous system; NaV = voltage-gated sodium channels; NK = neurokinin receptor; NMDA = N-methyl-D-aspartate; nTS = nucleus tractus solitarius; TRPA = transient receptor potential ankyrin; TRPV = transient receptor potential vanilloid
Smith JA, Woodcock A. *N Engl J Med.* 2016;375:1544-1551.

P2X3 Pathway



Vagal afferents transmit stimuli from the airways to the nTS & Para V in the brainstem. In the case of the P2X3 Pathway, one known stimuli is ATP. Neuronal signals are then transmitted causing throat irritation and urge to cough.

ATP = Adenosine Triphosphate; nTS = nucleus tractus solitarius; Para V = paratrigeminal nucleus

Adapted from Clinical Medicine 2016 Vol 16, No 6: s92-s97

Sensory Pathway Hyperexcitability

CONDITION/DISORDER

Headache/Migraine

Neuropathic Pain

Fibromyalgia

Itch

Chronic Cough

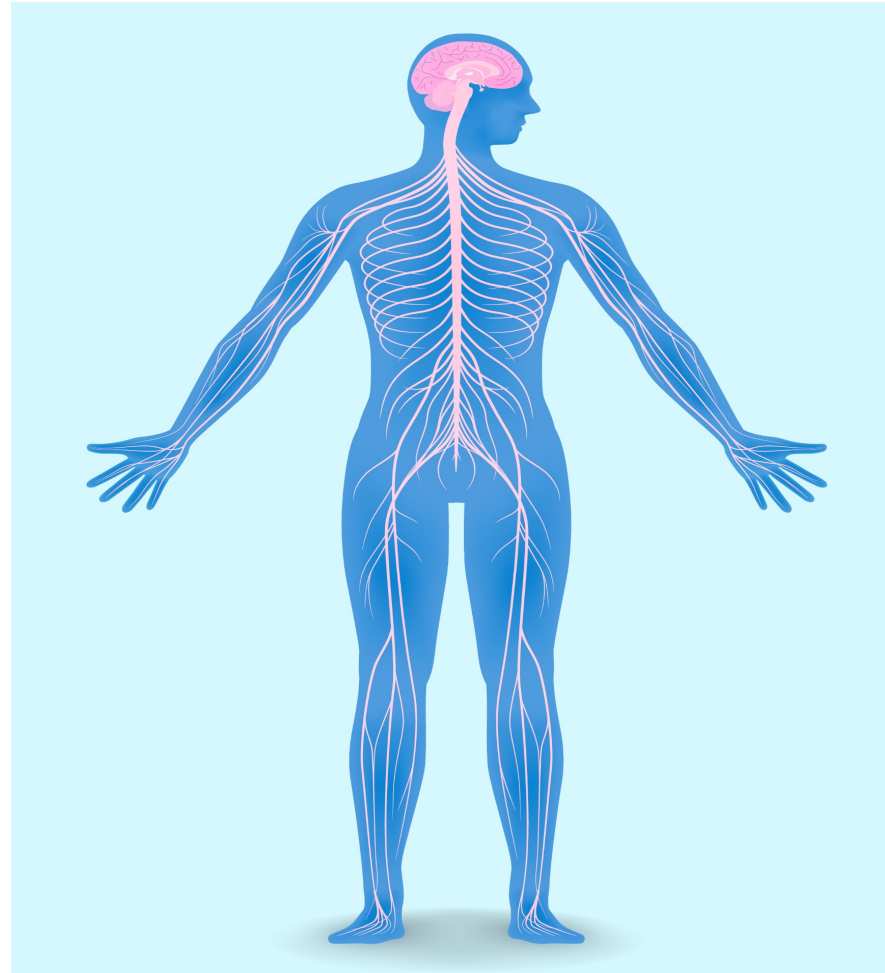
Bronchoconstriction

Hypertension

IBS-C/D

Urinary Urgency

Endometrial Pain



Cough Hypersensitivity Syndrome

- Is a condition not a symptom of a condition
- Is not anatomical/protective in nature
- Cough is irritative and originates from a neurogenic, nociceptive, type C pathway
- Increase “urge to cough” or globus sensation
- Leads to cough continuum from mild throat clear to spasmodic cough (men throat clear, women cough)
 - An “itch” or “tickle” on the back of the throat (Are we treating a cough or a tickle?)
 - Complaints of postnasal drip but NO mucous
 - Cough increases with talking (allotussia), exposure to irritants (hypertussia), and usually decreases/extinguishes at night

The Cough that Just Doesn't Go Away...

- **Chronic Cough:** cough with a duration of > 8 weeks
- **Refractory Chronic Cough (RCC):** a cough that persists despite guideline-based treatment for underlying conditions such as GERD, asthma, and rhinosinusitis
- **Unexplained Chronic Cough (UCC):** a cough that persists longer than 8 weeks, and remains unexplained after investigation

RCC and UCC may be due to Cough Hypersensitivity Syndrome

Current Chronic Cough Treatments- Neuromodulators*

Gabapentin* (1800 mg/d)

- RCT with 32 subjects with significant increase in LCQ vs placebo, reduced cough frequency over 1 hour of observation, and severity of cough
- AEs in 31% (nausea and fatigue) and effect waned after drug discontinuation. Also, cognitive changes, nausea or blurred vision.

Pregabalin* (300mg daily)

- Studied with speech therapy (SP) with an additive effect of pregabalin compared to SP alone
- Improved LCQ and cough severity, but no improvement in cough frequency
- AEs included dizziness, fatigue, cognitive changes, nausea or blurred vision

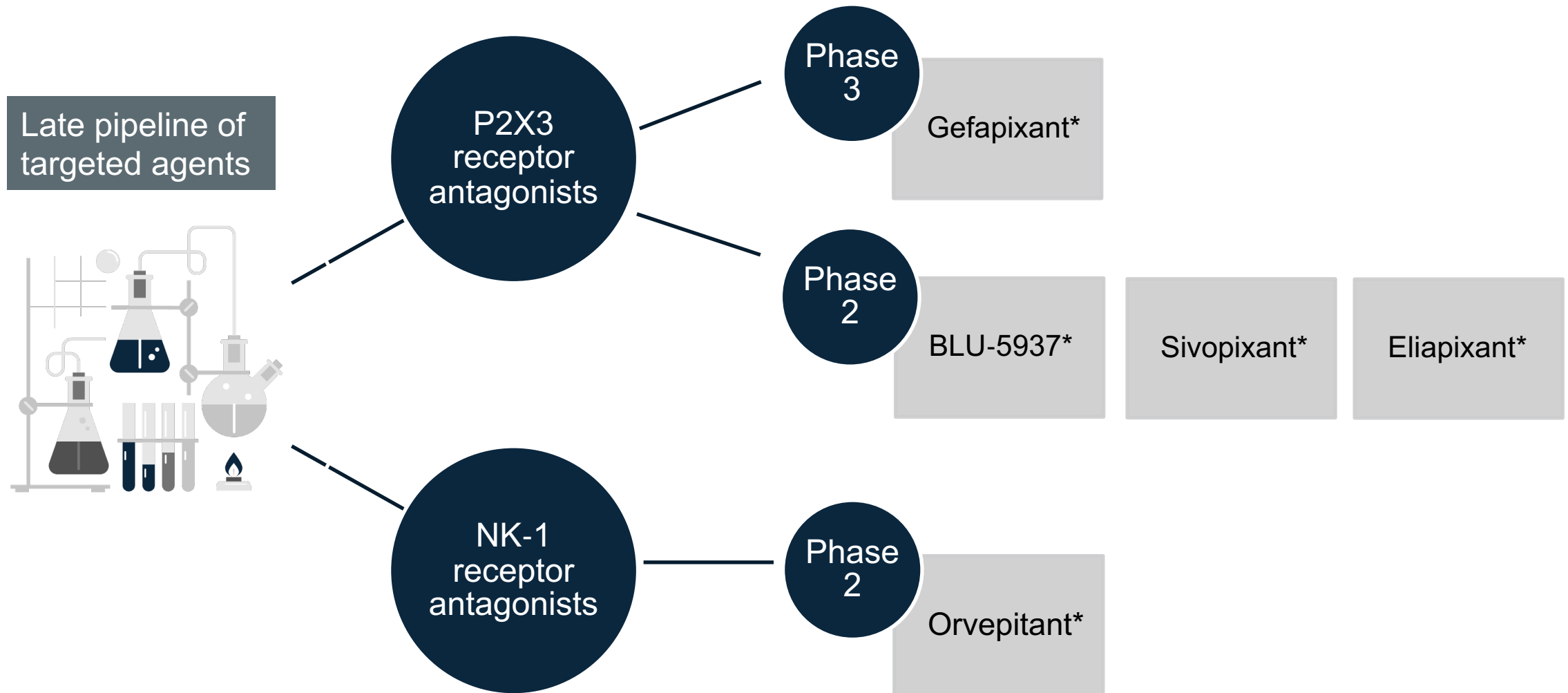
Morphine sulfate slow-release* (5-10 mg twice daily)

- RCT 27 subjects with significant increase in LCQ vs placebo and reduction in cough severity
- Side effects most noted were constipation and drowsiness
- Providers reluctant to treat with opioids long-term

* Not approved by the US FDA for the treatment of chronic cough

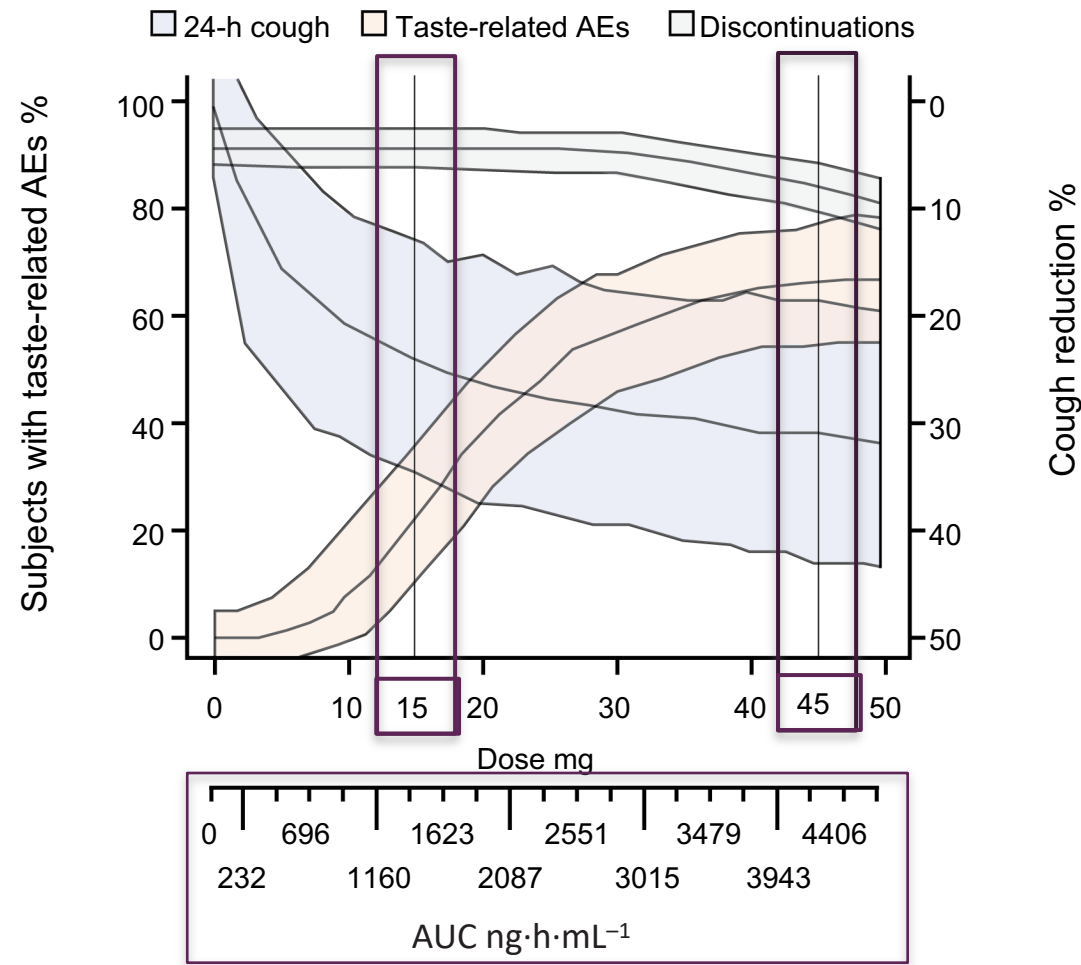
AEs= adverse events; d = day; LCQ= Leicester Cough Questionnaire; RCT= Randomized Controlled Trial
Morice AH, et al. *Eur Respir J.* 2020; 55(1):1901136.

Emerging Chronic Cough Treatments



* This agent is not currently approved by the FDA for the treatment of chronic cough
On PC. *Am J Manag Care.* 2020;26(Suppl 11):S239-S245.

Taste Disturbance vs Antitussive Effects of Gefapixant



Shaded areas represent 90% confidence intervals of 1000 trials

Gefapixant*: Efficacy and AE Studies

	COUGH-1 (Week 12)			COUGH-2 (Week 24)		
	Placebo	Gefapixant 15 mg	Gefapixant 45 mg	Placebo	Gefapixant 15 mg	Gefapixant 45 mg
Efficacy						
N included in analysis	222	227	217	419	415	409
Baseline geometric mean 24-hr cough frequency (coughs/hr)	22.83	19.86	18.24	19.48	19.35	18.55
Geometric mean 24-hr cough frequency at primary timepoint	10.33	9.66	7.05	8.34	8.1	6.83
Estimated relative reduction (%) (95% CI) vs placebo	--	1.58 (-16.12, 23.01) <i>p</i> = 0.872	-18.45 (-32.92, -.86) <i>p</i> = 0.041	--	-1.14 (-14.27, 14.02) <i>p</i> = 0.875	-14.64 (-26.07, -1.43) <i>p</i> = 0.031
Safety						
N included in summary (safety)	243	244	243	433	441	440
% Overall AEs	53%	56%	75%	73%	79%	87%
% Serious AEs	2%	3%	3%	4%	3%	3%
% Taste-related AE	3%	11%	58%	8%	20%	69%

Nearly 70% of treated patients had > than 30% reduction in cough

*Not currently approved by US FDA for chronic cough

CI = confidence interval; hr = hour

1. McGarvey L, et al. *Eur Resp J*. 2020;56(Suppl 64),3800. 2. Foo C, et al. Respiratory viruses in the “pre COVID-19” era. Virtual Congress; 2020.

Pharmacists to Enhance Care

- Counsel patients throughout the process
 - Provide OTC options when feasible
- Introduce patients to research trials
 - Build trust with patients
 - Explain why research is important
- Give patients hope for new medication therapies
 - Explain new mechanisms and promise of drug therapies

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- Talk to providers and patients about cough hypersensitivity as a major mechanism of CC that occurs with or without associated conditions like GERD, asthma, or rhinitis.
- Talk to providers about cough hypersensitivity in patients with CC (> than 8 weeks) with a mechanism related to an irritative, nociceptive, type C fiber pathway leading to an “urge to cough” or “tickle in the throat”.
- Talk to providers and patients about novel targeted agents in trials that offer promising hope as effective and tolerable treatments for CC

Don't Miss...

CME  **CAST** EPISODE 1

The Pharmacist's Role in Improving Early
Diagnosis for Patients with Chronic Cough

www.CMEOutfitters.com

Additional Resources

Visit www.cmeoutfitters.com
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certified educational activities