Nová anesteziologika; budou, nebo ne?

J. Málek

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Herold I. Nová farmaka v anesteziologii: pohled za horizont. PGM 2018;20(5):511-518

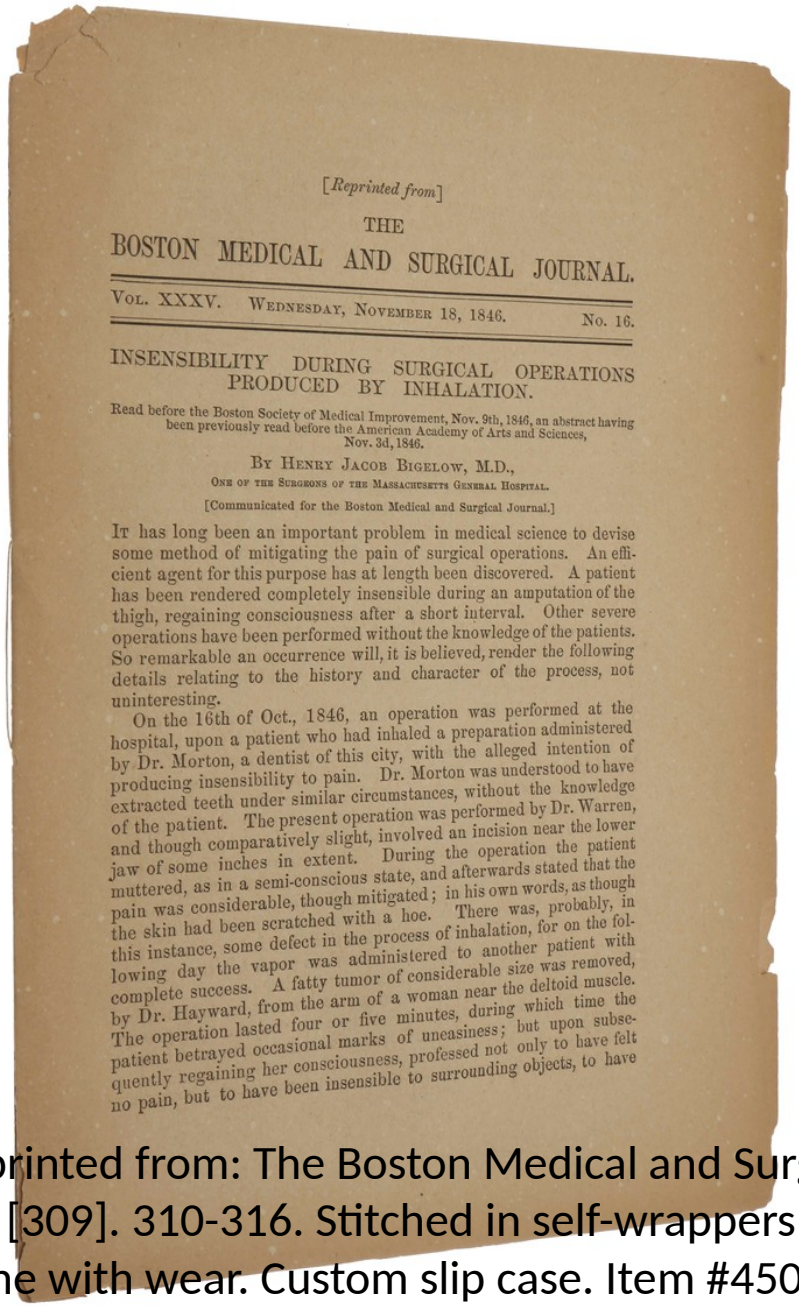
Anesthesiology's History

The Most Important Article in NEJM History

Posted by Karen Buckley • November 1st, 2012

Throughout the 200th anniversary year we have asked for your votes, and you have responded with a resounding favorite. Since the 1846 report from Boston surgeon Henry Jacob Bigelow, **"Insensibility during Surgical Operations Produced by Inhalation,"** so many of the significant advances we've seen rely on the use of anesthesia. It is difficult to imagine medicine today without it.

If you haven't read the original report yet, it's worth taking a few minutes to travel back to the mid-nineteenth century, when Bigelow wrote, "It has long been an important problem in medical science to devise some method of mitigating the pain of surgical operations. An efficient agent for this purpose has at length been discovered. A patient has been rendered completely insensible during an amputation of the thigh, regaining consciousness after a short interval. Other severe operations have been performed without the knowledge of the patients."



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THE

BOSTON MEDICAL AND SURGICAL JOURNAL.

VOL. XXXV. WEDNESDAY, NOVEMBER 18, 1846. No. 16.

INSENSIBILITY DURING SURGICAL OPERATIONS PRODUCED BY INHALATION.

Read before the Boston Society of Medical Improvement, Nov. 9th, 1846, an abstract having been previously read before the American Academy of Arts and Sciences, Nov. 3d, 1846.

BY HENRY JACOB BIGELOW, M.D.,
ONE OF THE SURGEONS OF THE MASSACHUSETTS GENERAL HOSPITAL.

[Communicated for the Boston Medical and Surgical Journal.]

IT has long been an important problem in medical science to devise some method of mitigating the pain of surgical operations. An efficient agent for this purpose has at length been discovered. A patient has been rendered completely insensible during an amputation of the thigh, regaining consciousness after a short interval. Other severe operations have been performed without the knowledge of the patients. So remarkable an occurrence will, it is believed, render the following details relating to the history and character of the process, not uninteresting.

On the 16th of Oct., 1846, an operation was performed at the hospital, upon a patient who had inhaled a preparation administered by Dr. Morton, a dentist of this city, with the alleged intention of producing insensibility to pain. Dr. Morton was understood to have extracted teeth under similar circumstances, without the knowledge of the patient. The present operation was performed by Dr. Warren, and though comparatively slight, involved an incision near the lower jaw of some inches in extent. During the operation the patient muttered, as in a semi-conscious state, and afterwards stated that the pain was considerable, though mitigated; in his own words, as though the skin had been scratched with a hoe. There was, probably, in this instance, some defect in the process of inhalation, for on the following day the vapor was administered to another patient with complete success. A fatty tumor of considerable size was removed, by Dr. Hayward, from the arm of a woman near the deltoid muscle. The operation lasted four or five minutes, during which time the patient betrayed occasional marks of uneasiness; but upon subsequently regaining her consciousness, professed not only to have felt no pain, but to have been insensible to surrounding objects, to have

The duration of the insensibility is another important element in the process. When the apparatus is withdrawn at the moment of unconsciousness, it continues, upon the average, two or three minutes, and the patient then recovers completely or incompletely, without subsequent ill effects. In this sudden cessation of the symptoms, this vapor in the air-tubes differs in its effects from the narcotics or stimulants in the stomach, and, as far as the evidence of a few experiments of Dr. Morton goes, from the ethereal solution of opium when breathed. Lassitude, headache and other symptoms lasted for several hours, when this agent was employed.

But if the respiration of the vapor be prolonged much beyond the first period, the symptoms are more permanent in their character. In one of the first cases, that of a young boy, the inhalation was continued during the greater part of ten minutes, and the subsequent narcotism and drowsiness lasted more than an hour. In a case alluded to before, the narcotism was complete during more than twenty minutes, the insensibility approached to coma.

Such cases resemble those before quoted from Christison and other authors, and show that the cessation of the inhalation, after it has been prolonged for a length of time, does not produce a corresponding cessation of the symptoms; while, if the inhalation is brief, the insensibility ceases in a short time. Recovery, in the latter case, is not improbably due to the complete and rapid elimination of the vapor from the lungs; the more gradual return of consciousness, in the former case, to the presence of a larger quantity of unexhaled particles. A fact mentioned by Christison bears upon this point. This author states that insensibility from the presence of a large quantity of alcohol in the stomach, often gives place to a complete and sudden return of consciousness, when the alcohol is removed by the stomach pump. It is probable that the vapor of the new preparation ceases early to act upon the system, from the facility with which it is exhaled.

The process is obviously adapted to operations which are brief in their duration, whatever be their severity. Of these, the two most striking are, perhaps, amputations and the extraction of teeth. In protracted dissections, the pain of the first incision alone is of sufficient importance to induce its use; and it may hereafter prove safe to administer it for a length of time, and to produce a narcotism of an hour's duration. It is not unlikely to be applicable in cases requiring a suspension of muscular action; such as the reduction of dislocations or of strangulated hernia: and finally it may be employed in the alleviation of functional pain, of muscular spasm, as in cramp and colic, and as a sedative or narcotic.

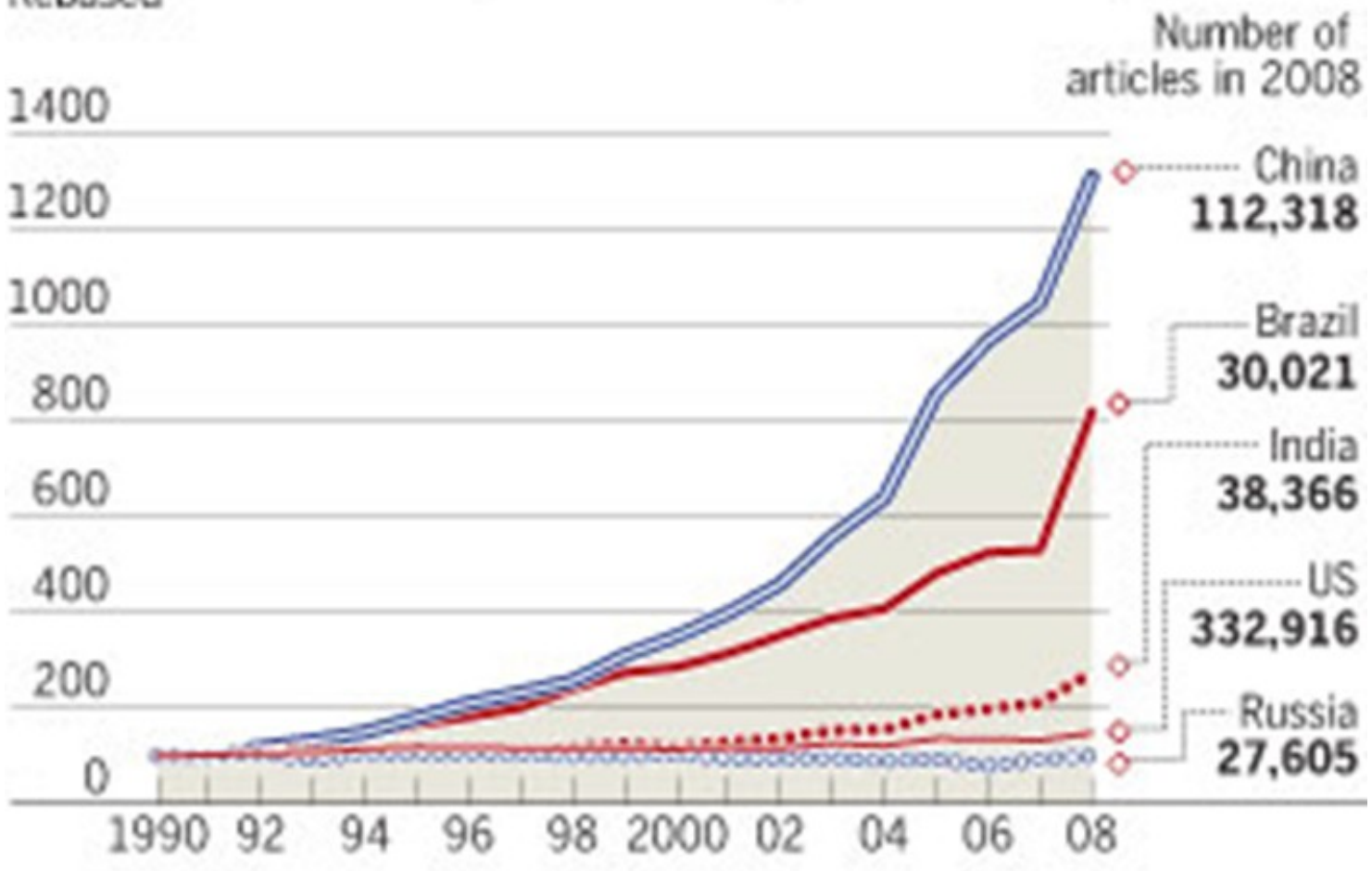
The application of the process to the performance of surgical operations, is, it will be conceded, new. If it can be shown to have been occasionally resorted to before, it was only an ignorance of its universal application and immense practical utility that prevented such isolated facts from being generalized.

Reprinted from: The Boston Medical and Surgical Journal, vol. XXXV, no. 16. 8vo (230 x 154 mm), pp. [309]. 310-316. Stitched in self-wrappers as issued, extremeties slightly frayed, corner and spine with wear. Custom slip case. Item #4503 **Price: $4,500.00**

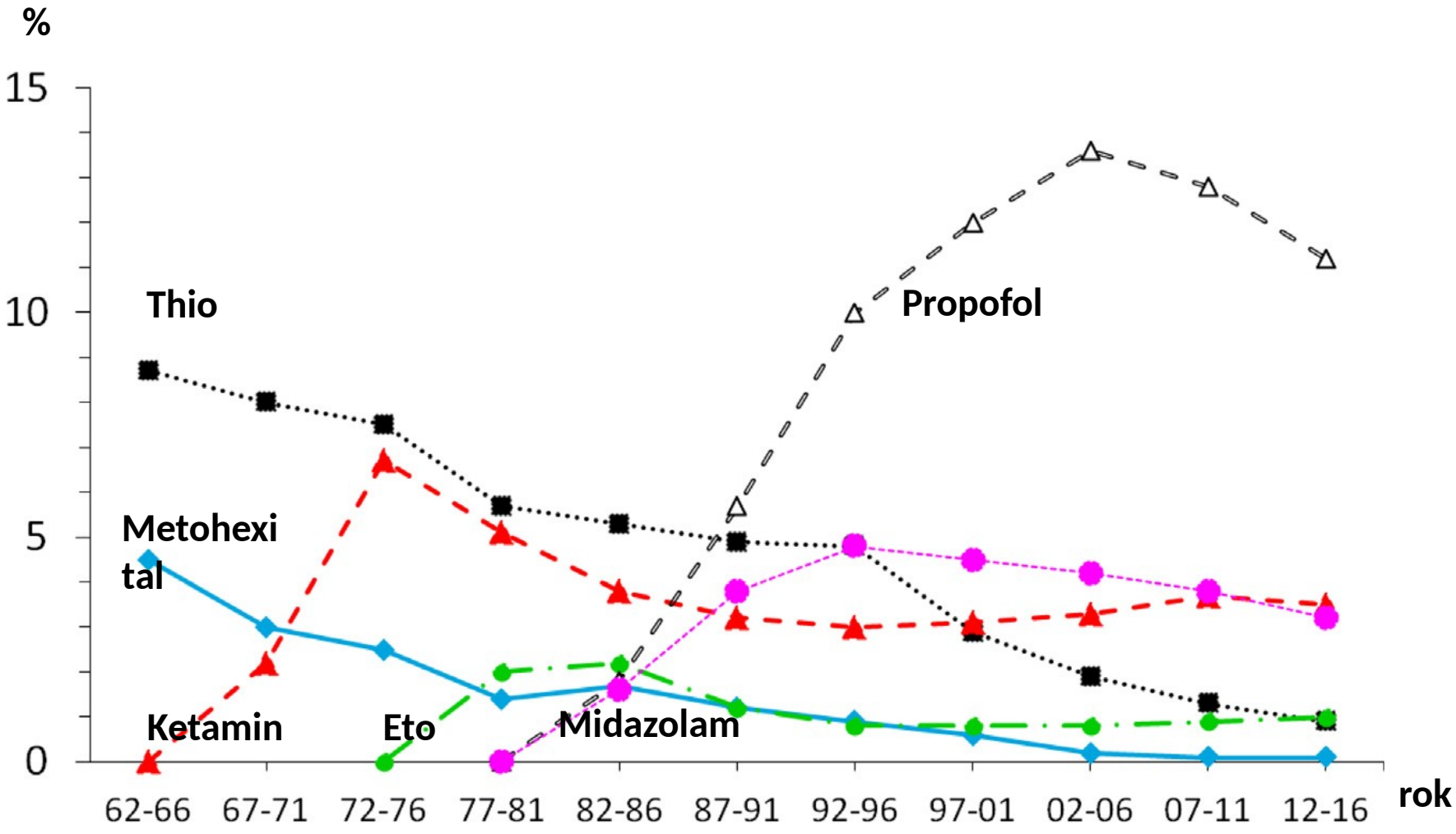
https://www.sophiararebooks.com/pages/books/4503/henry-jacob-bigelow/insensibility-during-surgical-operations-produced-by-inhalation

Growth of articles published in peer-reviewed journals

Rebased

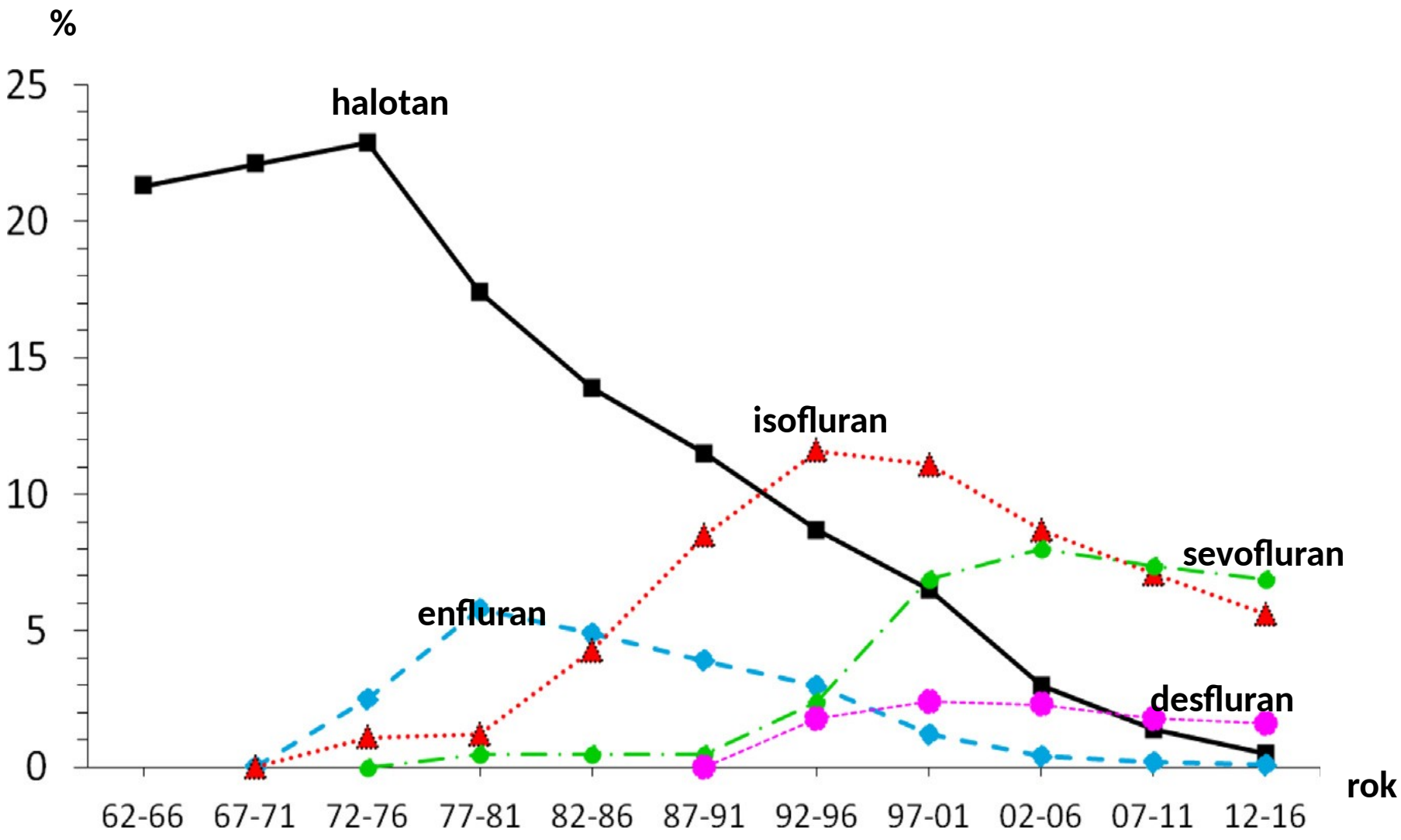


Sources: Thomson Reuters; Web Science Database



Index popularity jednotlivých i.v. anestetik (%)

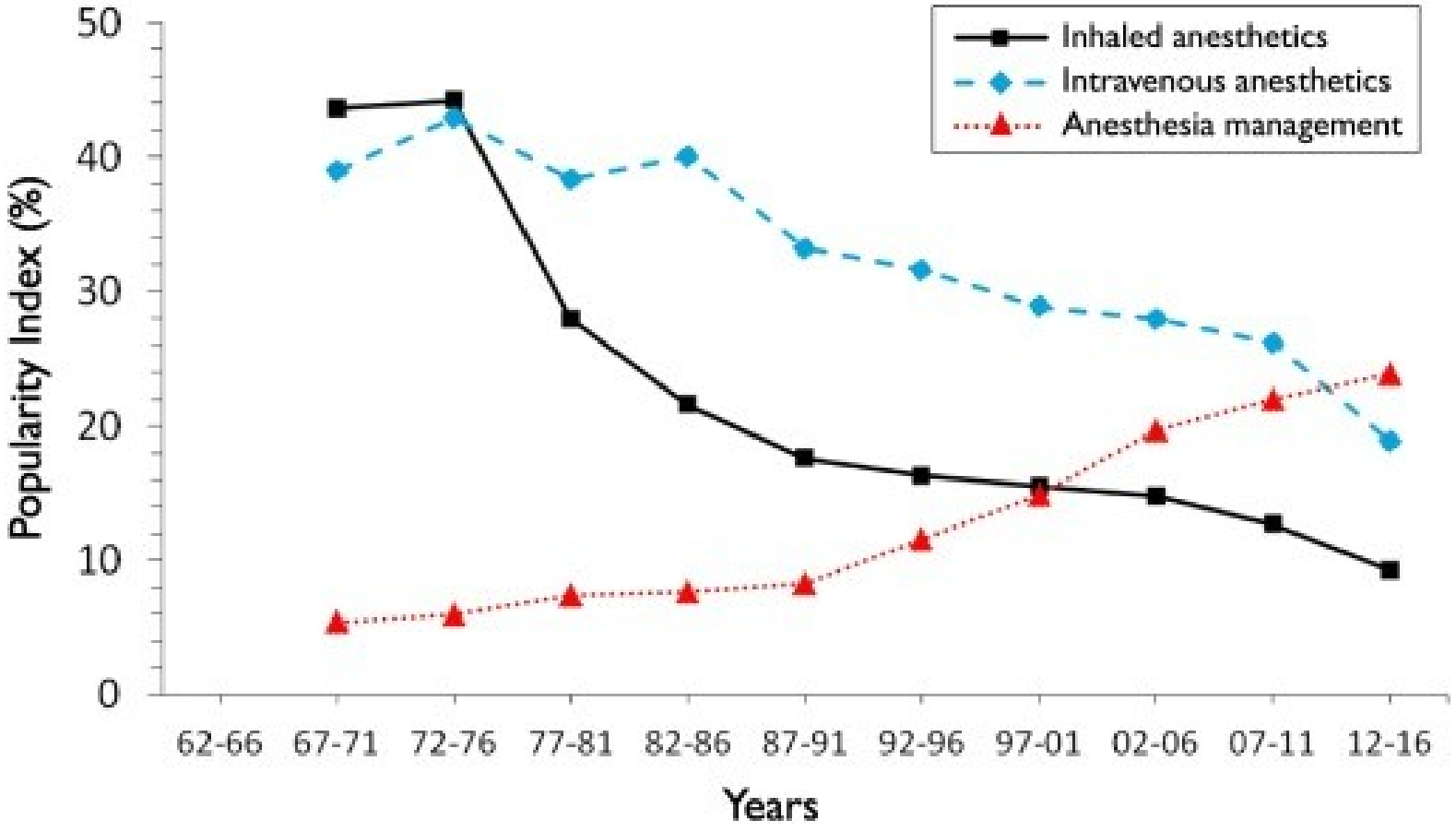
Correll DJ et al., 2018

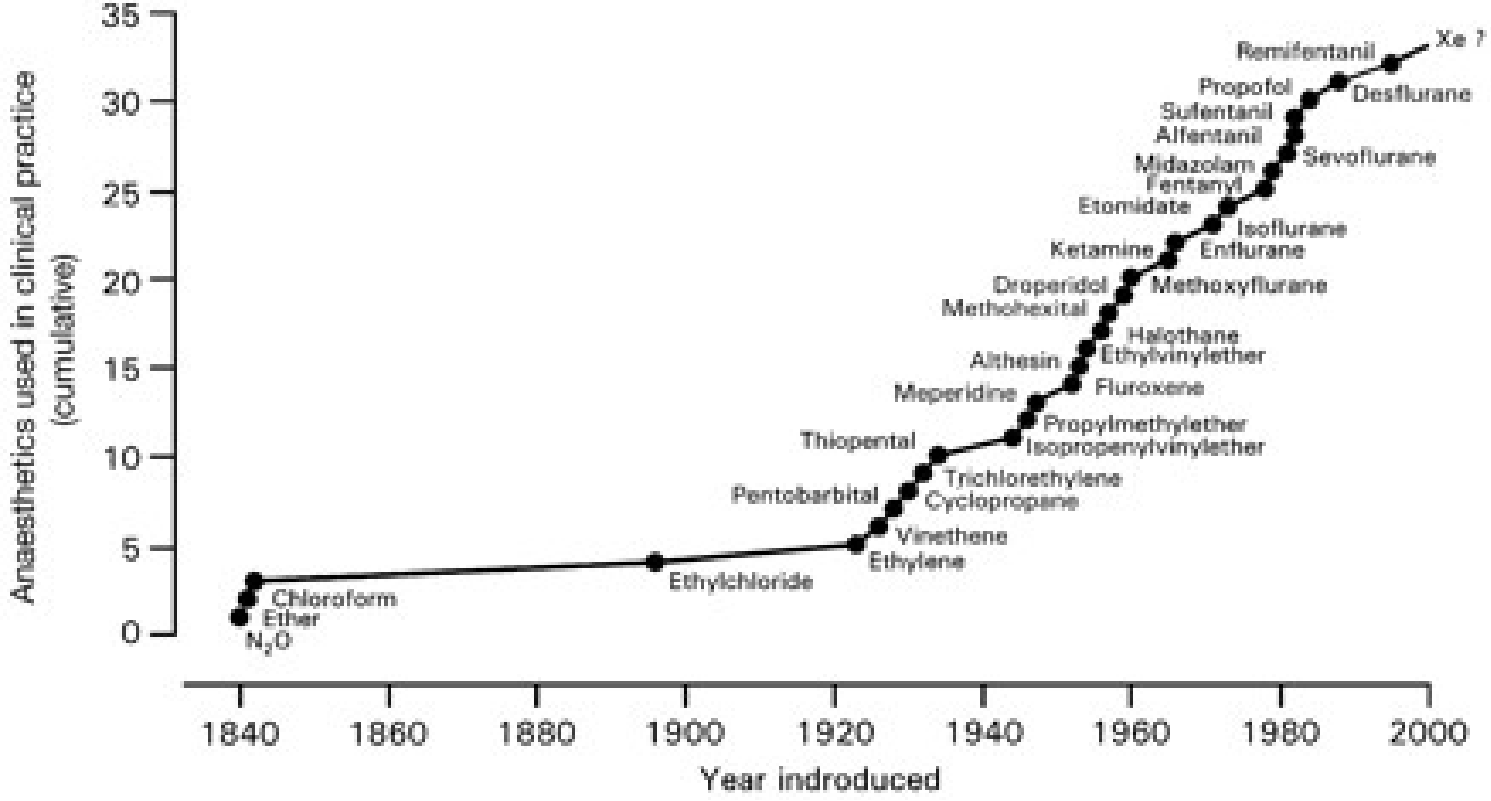


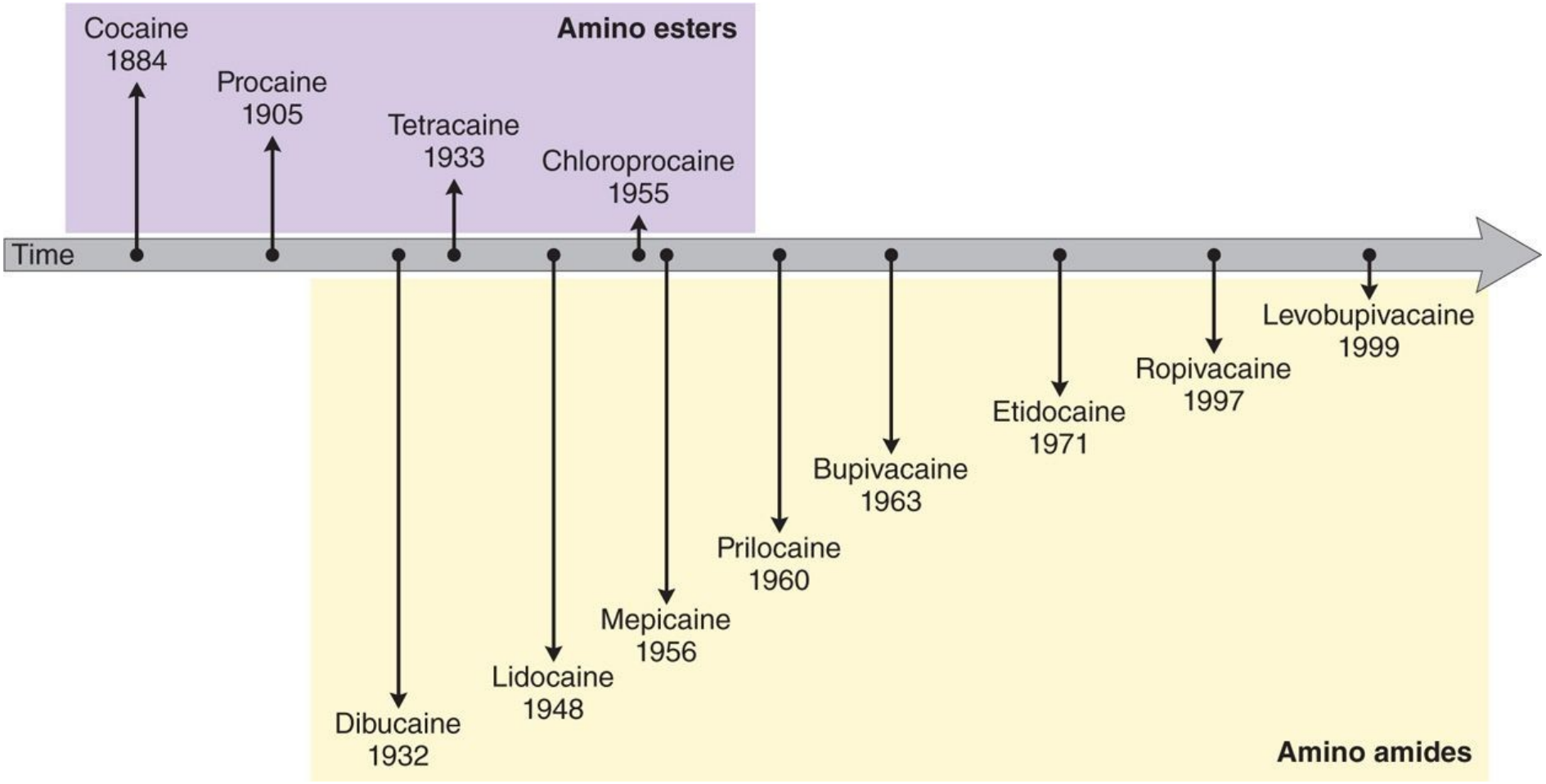
Index popularity jednotlivých inhal. anestetik (%)

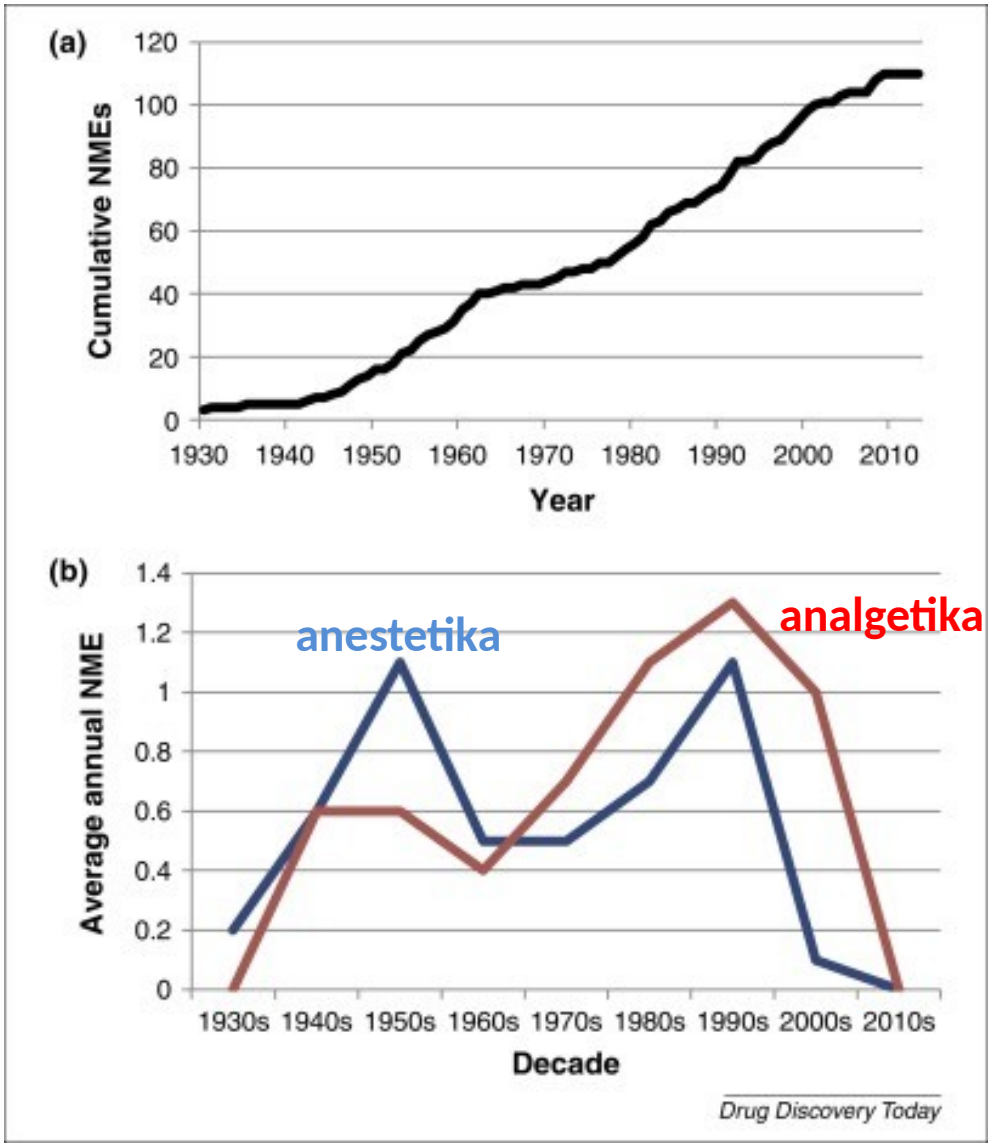
Correll DJ et al., 2018

Nové vědecké články




Anaesthetics used in clinical practice (cumulative)
35
30
25
20
15
10
5
0
1840
1860
1880
1900
1920
1940
1960
1980
2000
Year indroduced
Remifentanil
Xe ?
Propofol
Desflurane
Sufentanil
Alfentanil
Midazolam
Sevoflurane
Fentanyl
Etomidate
Isoflurane
Ketamine
Enflurane
Droperidol
Methoxyflurane
Methohexital
Halothane
Althesin
Ethylvinylether
Meperidine
Fluroxene
Propylmethylether
Thiopental
Isopropenylvinylether
Trichlorethylene
Pentobarbital
Cyclopropane
Vinethene
Ethylene
Ethylchloride
Chloroform
Ether
N_2O


Amino esters
Cocaine
1884
Procaine
1905
Tetracaine
1933
Chloroprocaine
1955
Time
Dibucaine
1932
Lidocaine
1948
Mepicaine
1956
Prilocaine
1960
Bupivacaine
1963
Etidocaine
1971
Ropivacaine
1997
Levobupivacaine
1999
Amino amides



Kumulativní počet nových molekul pro analgezii a anestezii

Počet schválených nových molekul pro analgezii a anestezii za dekádu

Kinch MS, 2014

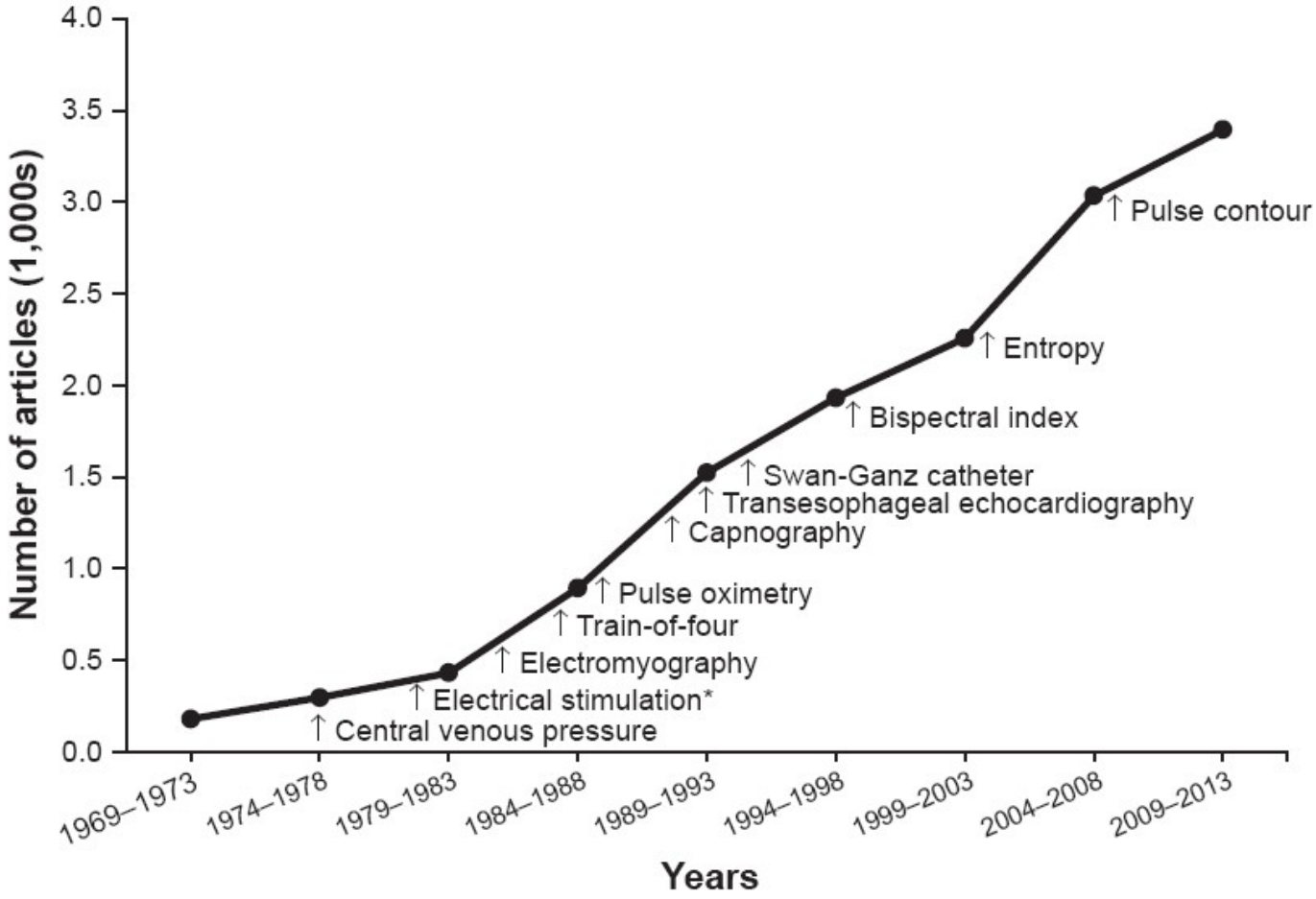
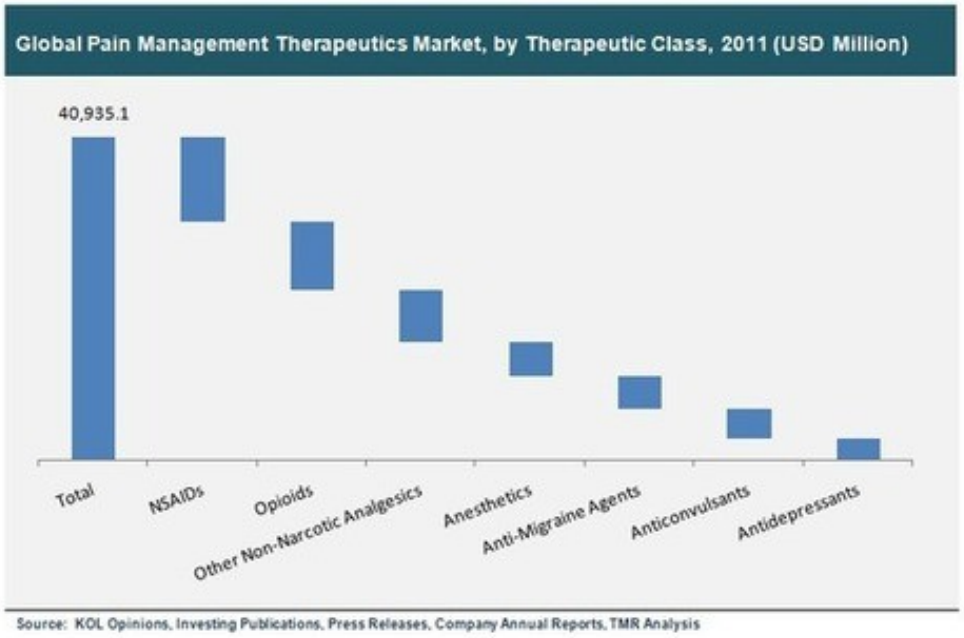


Figure 1 Five-year growth of all articles on anesthesia monitoring.

Notes: ↑Indicates the time of initial growth in publications on a related specific topic of anesthesia monitoring. *Indicates the topic of electrical nerve stimulation for neuromuscular monitoring.

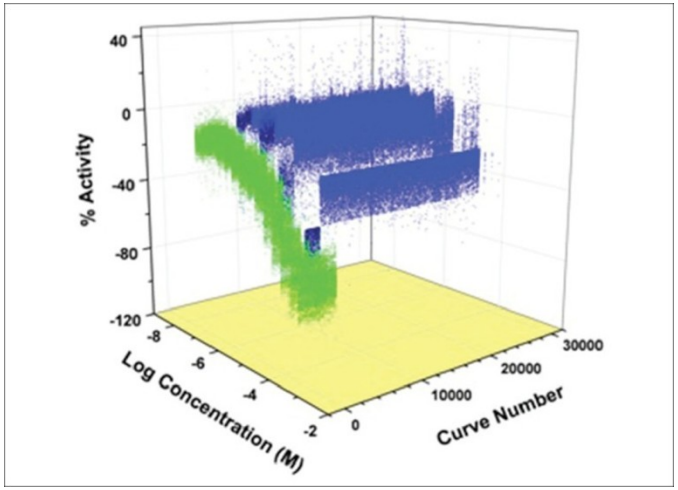
Vyplatí se nová anestetika? Tanious MK et al., 2017

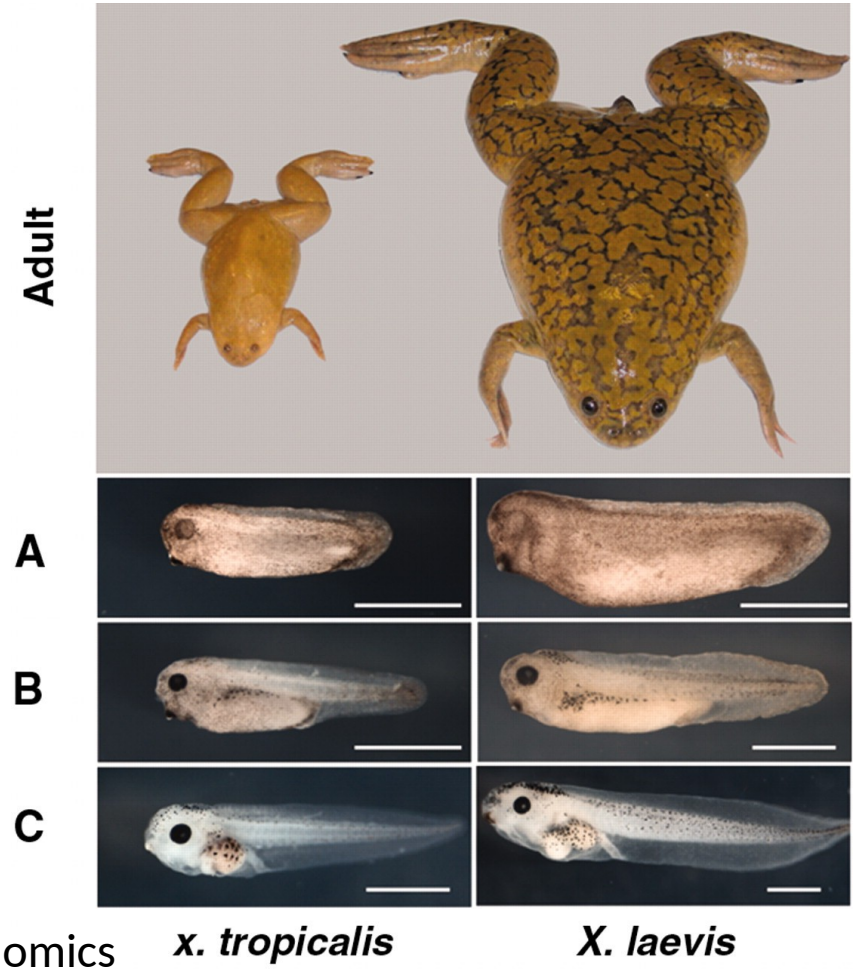
- Proces vývoje do schválení cca 10 let
- Náklady na vývoj nového léku 2 500 000 000 USD
- Z léků, které prošly fází 1, je schváleno k užití 10 %
- Náklady po schválení 2 800 000 000 USD



Hledání nových molekul Chitilian HV et al., 2013

- Vztah mezi strukturou molekuly a cílem (vazba na apoferitin, inhibice fluorescence)
- Sériové testování
  - (hlodavci)
  - Pulci r. Xenophus (drápatka)





Inhibice fluorescence v National Chemical Genomics Centre, 25 000 sloučenin, z nich 2 500 vysoce aktivních

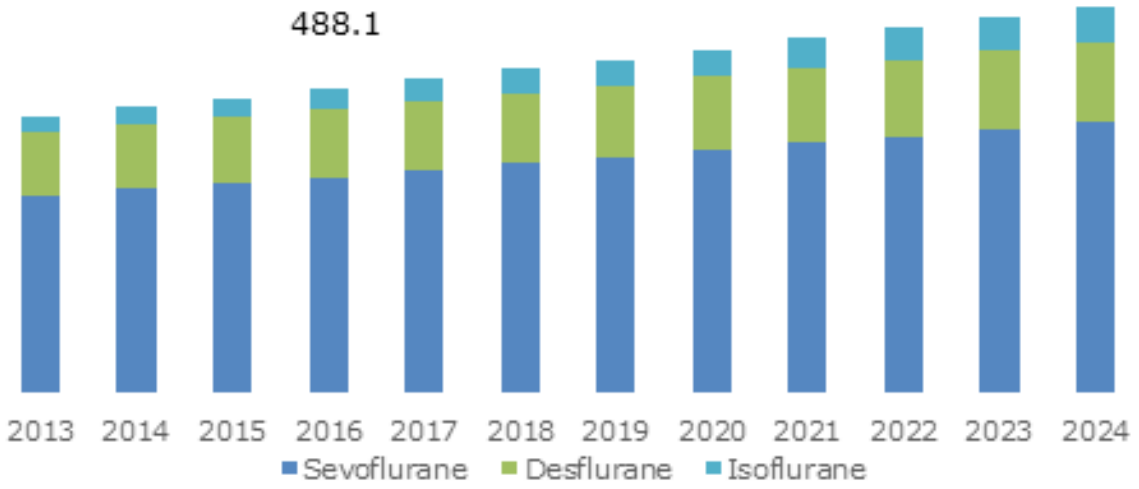
Recentní trend – modifikace již užívaných látek

„Soft“ (retrometabolická) modifikace

	Name	Year of First Clinical Study	Year of FDA Approval	Relationship to the Modified Parent Anesthetic	Parent Anesthetic, Year of Introduction
1	Eltanolone (5β-pregnanolone)	1990 [10,11]	–	5β-Pregnanolone, a steroid anesthetic (stemmed from the paper by Selye in 1941)	–
2	Ketamine S^+ enantomer	1994 [12] 2008 [13]	–	The S^+ isomer of ketamine with a faster recovery profile	Ketamine (racemic mixture) 1966
3	ORG-21465	1997 [14]	–	A water-soluble steroid	Althesin 1972
4	Fospropofol (Aquavan)	2005 [15]	2008	A water-soluble prodrug of propofol	Propofol 1977
5	ORG-25435	2010 [16]	–	A water-soluble steroid	Althesin 1972
6	Remimazolam (CNS 7056)	2012 [17]	–	A benzodiazepine designed to be rapidly metabolized by body esterases	Midazolam 1979
7	Phaxan (alfaxalone/ cyclodextrin)	2015 [18]	–	Alfaxalone/cyclodextrin formulation, one of two steroids representing althesin (alfaxalone/alfadolone)	Althesin 1972
8	AZD-3043 (THRX-918661)	2015 [19]	–	A eugenol compound, designed to be rapidly metabolized by body esterases	Propanidid 1964
9	ABP-700	2015 [20]	–	One of the etomidate analogs with reduced effect on adrenocortical function and rapid metabolism	Etomidate 1973

Vlassakov K et al., 2016

Předpokládaný růst trhu s inhalačními anestetiky (publ. 2017)

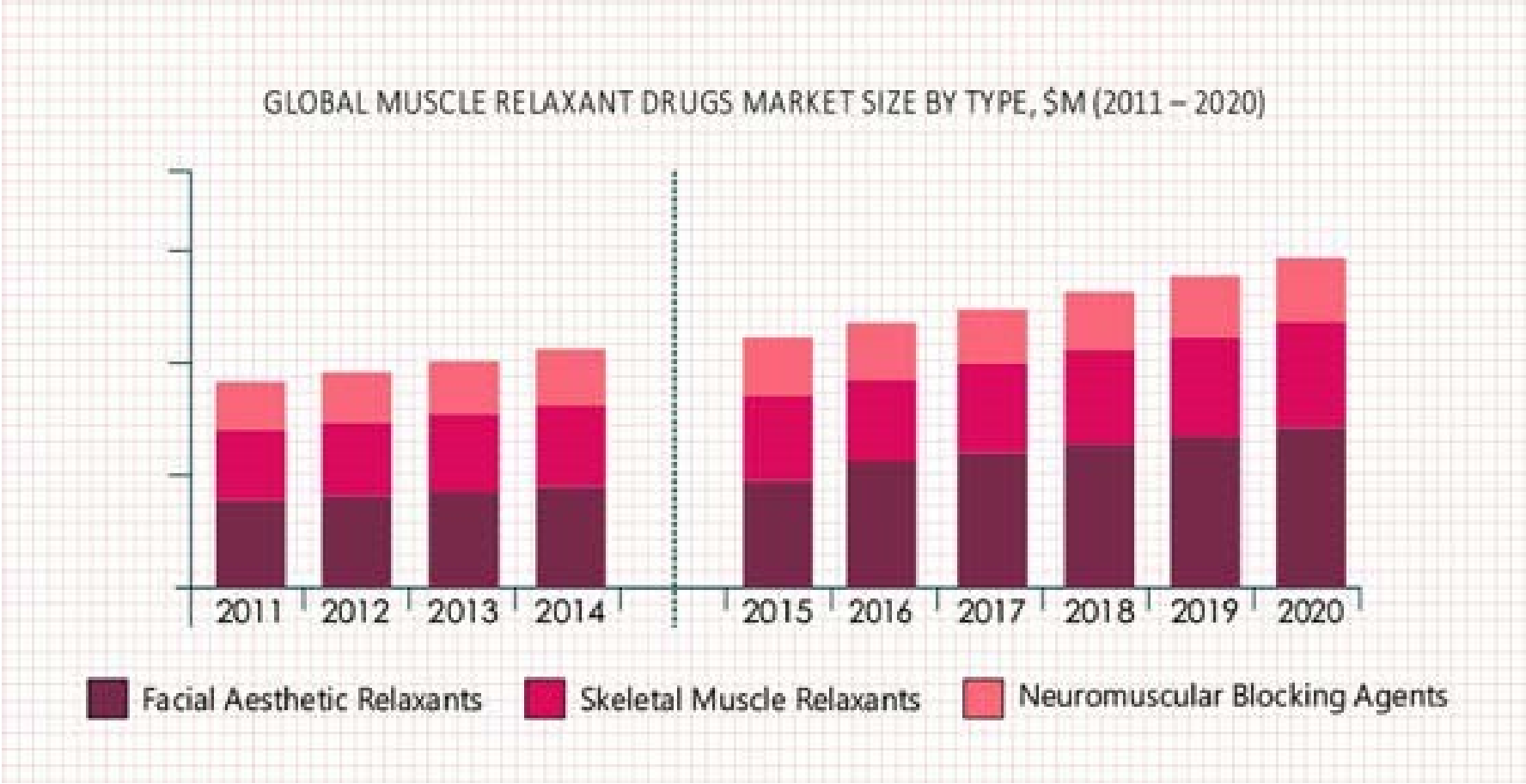


U.S. Inhalation Anesthesia Market, By Product, 2013 - 2024 (USD Million)

Anesthesia Drugs Market Segmentation And Analysis By Recent Trends, Development And Growth By Trending Regions 2018. Rodriguez M, 2018

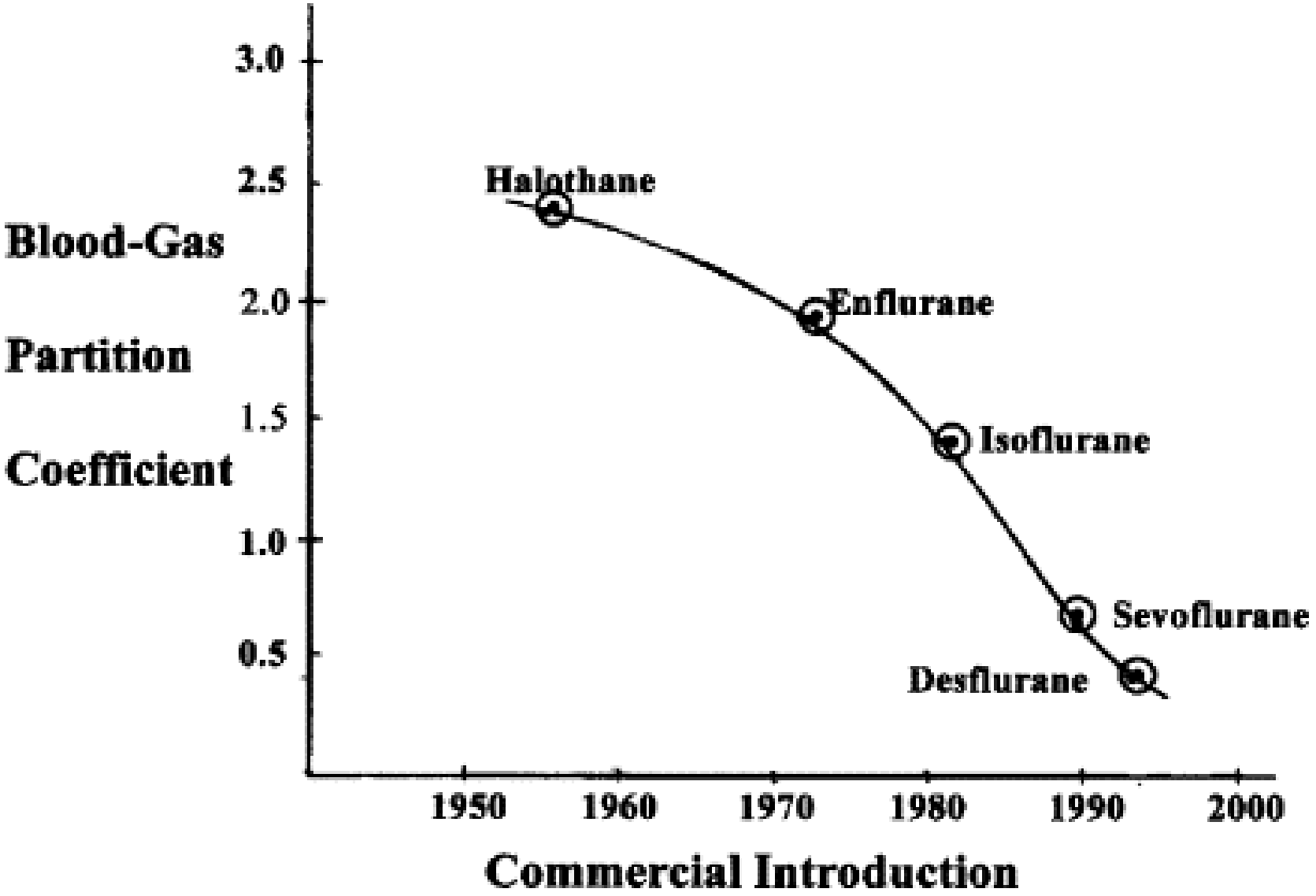
- Celková anestetika tvoří největší podíl růstu, t.č. nejvíce Indie
- Předpoklad nových preparátů – deriváty propofolu, midazolamu a etomidátu

Předpokládaný růst trhu se SR



Nová inhalační anestetika?

Je ještě co zlepšovat?



Inhalační anestetika – nové molekuly? Terrell RC,2008

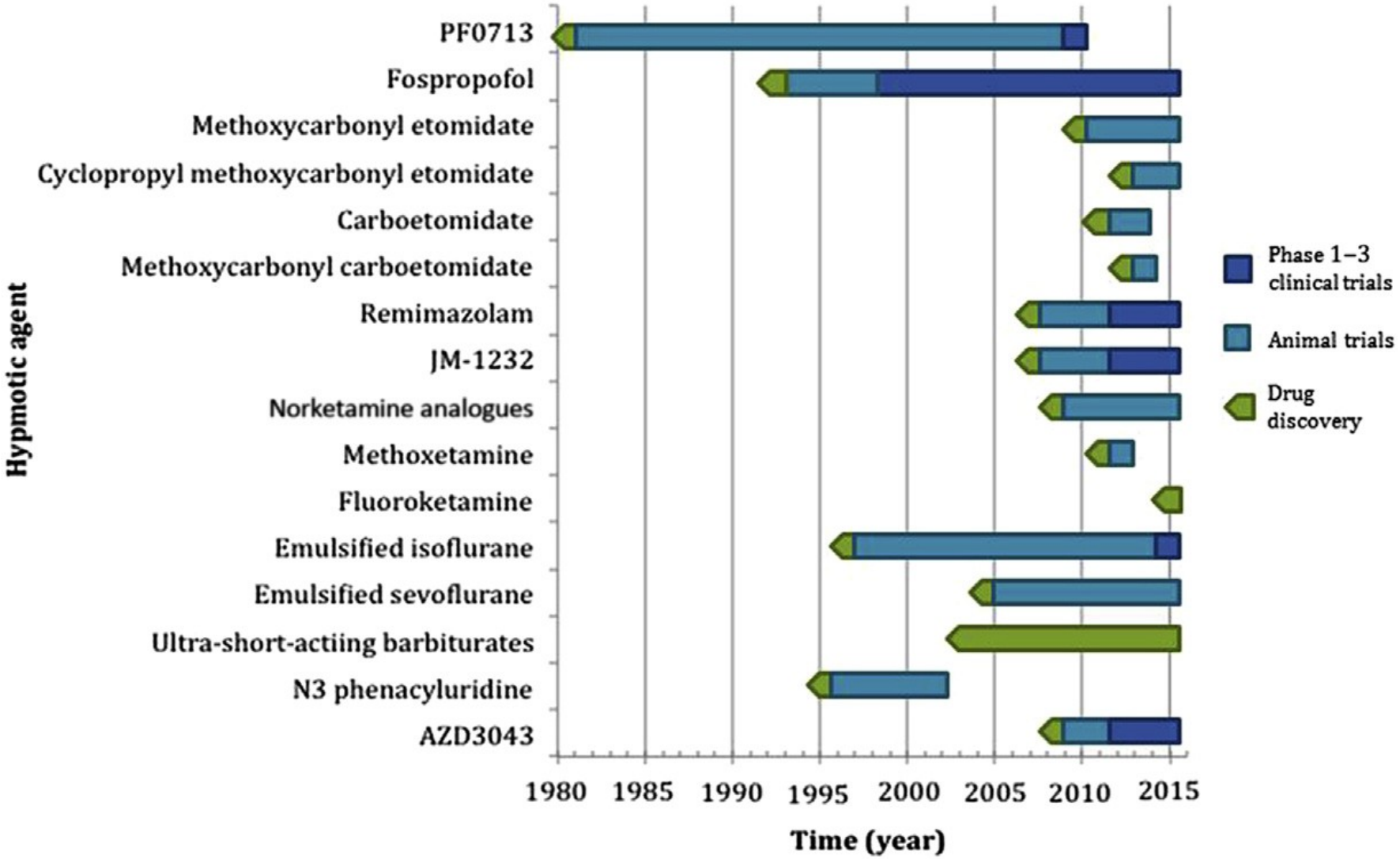
- Snadná odpařitelnost –max. 4 C atomy
- Nehořlavost – limituje počet H atomů
- Stabilita v odpařovači – eliminuje skupiny CH_2CLO-
- Laciná masová produkce (> 2 000 t/rok)

- Po aplikaci výše uvedených kritérii zbývá z cca 4 000 sloučenin asi 250, z nichž téměř všechny byly testovány

Nová i.v. anestetika?

Suspektní nová intravenózní anestetika

Tanious MK et al., 2017



Deriváty propofolu Feng AY et al., 2017

- Cíle: odstranit nestabilitu emulze, hyperlipidemii, KV NÚ, bolest při inj., riziko kontaminace a propofolový sy
- PF0173: rychlý nástup, kardiovaskulární stabilita, delší účinek než propofol – fáze 1, další osud neznámý
- Změna nosného vehikula
  - Emulgované roztoky s jiným vehikulem – studie přerušeny
  - Vodné roztoky
    - Cyklodextriny – vývoj přerušen pro bolestivost
    - Micelové formy – experimenty na zvířatech
- Prodrugs rozpustné ve vodě
  - Fospropofol – schválen, ale t.č. nevyráběn
  - HX0507 a HX0969w ve fázi experimentu

Deriváty midazolamu a GABAergní látky

- Cíle: kratší účinek, nezávislost na P450
- Remimazolam: hydrolýza nespec. esterázami, nástup 1 – 3 min., contex s. h. 7 min. - fáze 3
- JM-1232(-) GABA-ergní látka s rychlým nástupem účinku a zotavením, fáze 2 Kodai Ikemoto et al., 2015, Sneyd JR et al., 2012

Analoga etomidátu Valk BI et al., 2018

- Cíl: krátký účinek, bez adrenokortikálního efektu
- Metoxycarbonyl (MOC)-etomidát; rychlý nástup účinku, možnost kumulace – vývoj asi zastaven
- Carboetomidát – pomalejší nástup i odeznění, bez AC efektu – experiment na zvířeti
- Metoxycarbonyl carboetomidát – podobný caboetomidátu, rychleji metabolizován
- Cyklopropyl MOC etomidát (CPMM, též ABP-700); rychlý nástup účinku, delší efekt, než etomidát, ale contex sens. lifetime 4 min., bez adrenokortikálního efektu, fáze 2

Deriváty ketaminu

- Cíl: rychlý nástup, krátký účinek, absence psychomimetických účinků
- S(+)-ketamin – registrován v řadě zemí
- Methoxetamin – t.č. jen designerská droga (MXE, Mexxy), několik úmrtí *https://psychonautwiki.org*
- Fluoroketamine – rekreační droga? *https://psychonautwiki.org*
- Esterová analoga norketaminu; rychlý nástup i odeznění účinku, snad menší výskyt psychomimetických účinků – experiment na králících Harvey M et al., 2015

Emulgovaná inhalační anestetika

- Cíl: rychlý nástup, absence odpařovače
- Emulgovaný isofluran – fáze 1
- Emulgovaný sevofluran – experiment na zvířeti
- Nevýhody
  - Bolest při aplikaci
  - Pach

Ultrakrátce působící barbituráty

Tanious MK et al., 2017

- Cíle: rychlý nástup i odeznění účinku eliminací, nejen redistribucí, méně KV účinků
- Esterové deriváty kyseliny barbiturové a thiobarbiturové –patenty na molekuly 2002 a 2010, další osud neznámý

Nové látky

- N3 fenacyluridin – vývoj zastaven pro NÚ v 2008
- JM-1232(-) GABA-ergní látka s rychlým nástupem účinku a zotavením, fáze 2 Kodai Ikemoto et al., 2015, Sneyd JR et al., 2012
- AZD 3043, podobný propanididu – fáze 2
- Phaxan (alfaxalon), podobný propofolu bez oběh. deprese a bolesti – fáze 2

Nová svalová relaxancia?

Honba za „ideálním SR“

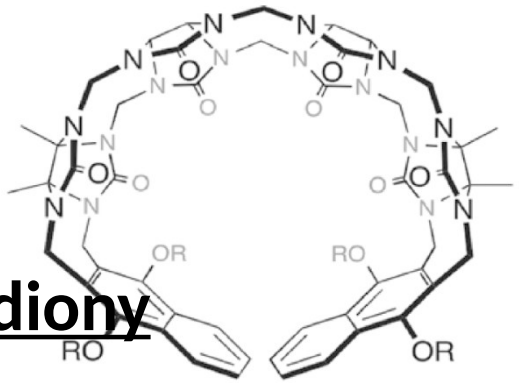
- Ultrakrátký nástup účinku
- Variabilní farmakokinetika odpovídající požadované délce akce (ultrakrátké trvání účinku)
- Selektivní účinek na N Ach receptory (žádné muskarinové vedlejší účinky)

Očekávání (a zklamání?)

- 1980 atracurium a vecuronium symbolicky pohřbívají suxamethonium, z dálky přihlíží pancuronium, metocurin, d-tubocurarin
- 2010:
  - atracurium → cis-atracurium
  - vecuronium → rocuronium
  - v propadlišti zmizely docaxurium a rapacuronium
  - používáme stále suxamethonium a neostigmin

Svalová relaxancia Heerdt PM et al. 2015, de Boer HD et al., 2018

- Cíl: NDSR, rychlý nástup, bez uvolnění histaminu, krátký účinek nebo antagonizace bez efektu na Ach receptory
- Gantakurium – ultrakrátké SR, antagonizace L-cysteinem (endogenním), uvolnění histaminu ve větších dávkách
- CW 002 – modifikace gantakuria, delší účinek, neuvolňuje histamin – fáze 1
- CW 011 – experimenty na zvířatech

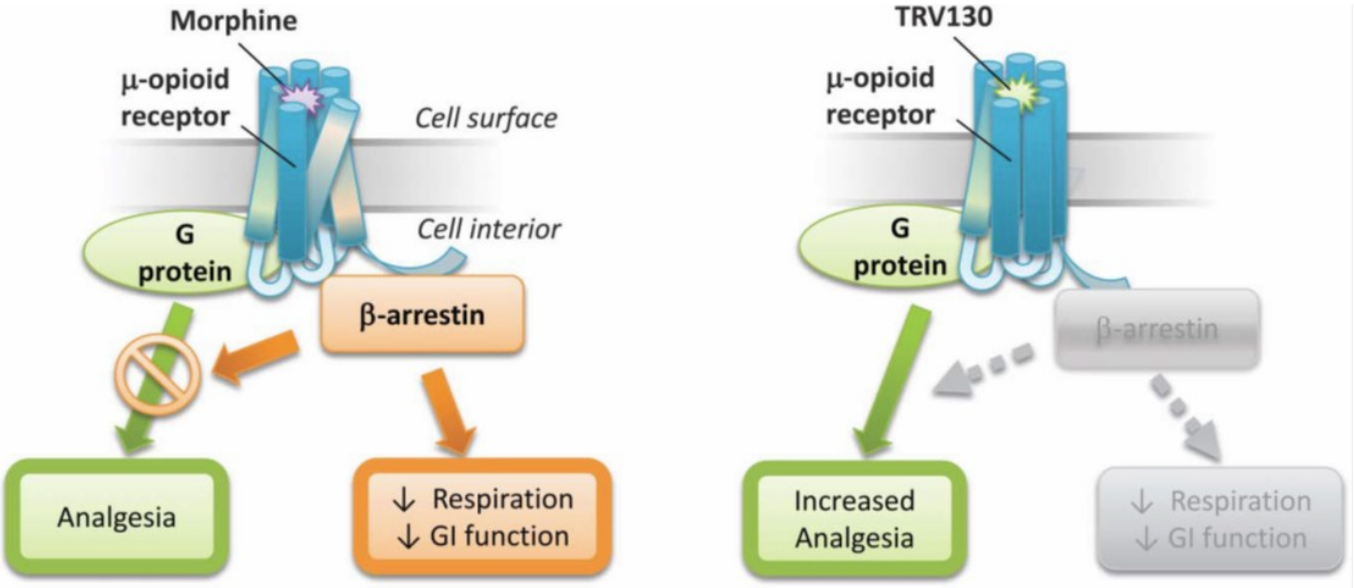


- Nástupci sugammadexu: L cystein, **calabadiony**

Nové opioidy?

Opioidy

- CR845 (Difelikefalin) i.v. i p.o., agonista periferních kappa receptorů, bez průniku do CNS a bez potenciálu pro dechovou depresi, abuzus, PONV, svědění – fáze 3. Pouze firemní publikace Hesselink JMK, 2018
- Oliceridin – selektivní agonista na GP části mí receptoru – fáze 2



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