

Naloxone: Effects and Side Effects

Gregory W. Terman M.D., Ph.D.

Professor

**Department of Anesthesiology and Pain Medicine
and the Graduate Program in Neurobiology**

Mayday Pain and Society Fellow

University of Washington

Seattle, Washington 98195

gwt@u.washington.edu



Naloxone: Effects and Side Effects

- ◆ Specificity
- ◆ Toxicology
- ◆ Unmasking Disease

Naloxone: Effects and Side Effects

ARTICLE

doi:10.1038/nature10954

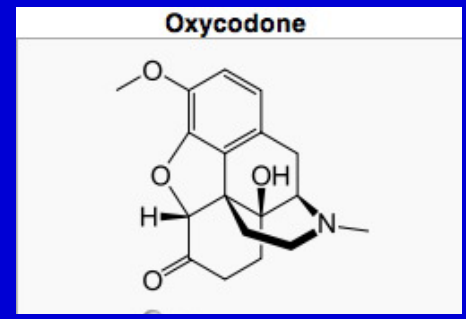
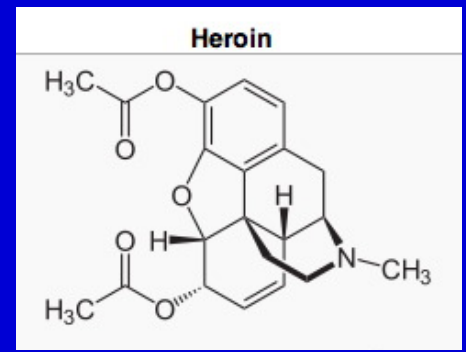
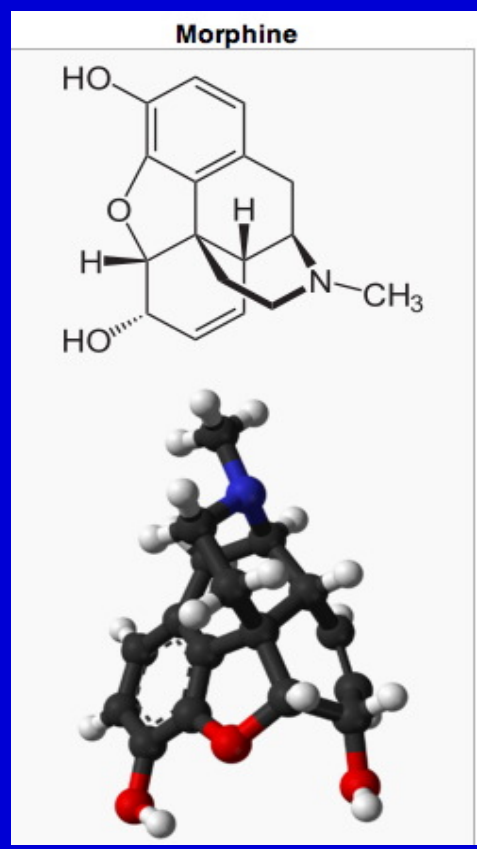
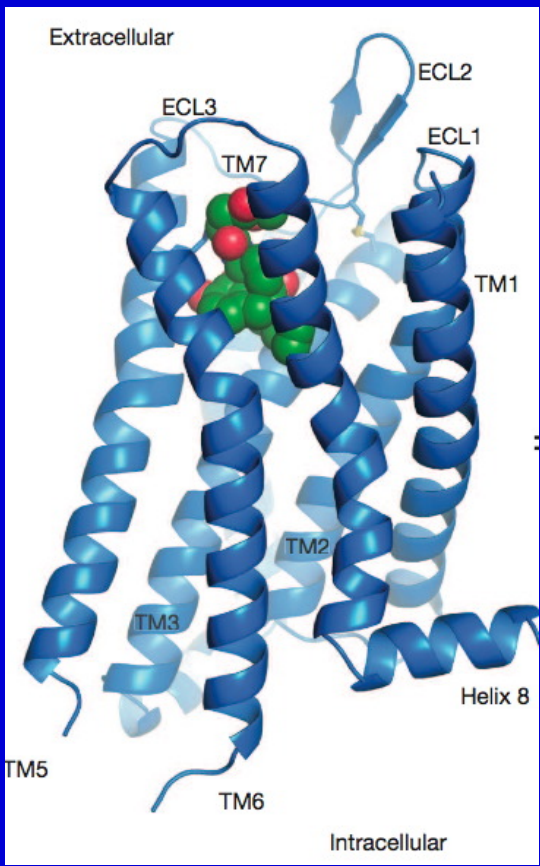
Crystal structure of the μ -opioid receptor bound to a morphinan antagonist

Aashish Manglik¹, Andrew C. Kruse¹, Tong Sun Kobilka¹, Foon Sun Thian¹, Jesper M. Mathiesen¹, Roger K. Sunahara², Leonardo Pardo³, William I. Weis^{1,4}, Brian K. Kobilka¹ & Sébastien Granier^{1,5}

Opium is one of the world's oldest drugs, and its derivatives morphine and codeine are among the most used clinical drugs to relieve severe pain. These prototypical opioids produce analgesia as well as many undesirable side effects (sedation, apnoea and dependence) by binding to and activating the G-protein-coupled μ -opioid receptor (μ -OR) in the central nervous system. Here we describe the 2.8 Å crystal structure of the mouse μ -OR in complex with an irreversible morphinan antagonist. Compared to the buried binding pocket observed in most G-protein-coupled receptors published so far, the morphinan ligand binds deeply within a large solvent-exposed pocket. Of particular interest, the μ -OR crystallizes as a two-fold symmetrical dimer through a four-helix bundle motif formed by transmembrane segments 5 and 6. These high-resolution insights into opioid receptor structure will enable the application of structure-based approaches to develop better drugs for the management of pain and addiction.

Opium extracts from the plant *Papaver somniferum* have been used that it may be possible to develop safer and more effective therapeutic

Naloxone: Effects and Side Effects



Naloxone: Effects and Side Effects

N-ALLYLNOROXYMORPHONE: A NEW POTENT NARCOTIC ANTAGONIST

By FRANCIS F. FOLDES, M.D.*

DIRECTOR, DEPARTMENT OF ANESTHESIA, MERCY HOSPITAL
CLINICAL PROFESSOR OF ANESTHESIOLOGY, UNIVERSITY OF PITTSBURGH

JOHN N. LUNN, M.B.
MERCY HOSPITAL

JAMES MOORE, M.D.
VISITING RESEARCH FELLOW, DEPARTMENT OF ANESTHESIA, MERCY HOSPITAL

AND

IAN M. BROWN, M.B.

(From the Departments of Anesthesiology of Mercy Hospital and the University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania)

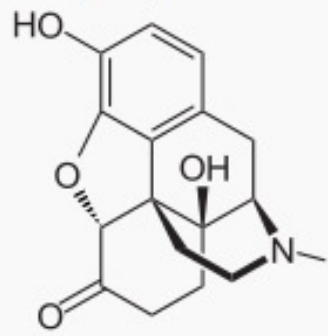
It has been known since 1915, when Pohl¹⁷ described the antagonistic effect of N-allylcodeine on the codeine-induced respiratory depression that N-allyl derivatives of narcotic analgesics are capable of antagonizing narcotic-induced respiratory depression

production of controllable apnea during anesthesia (Foldes *et al.*⁷).

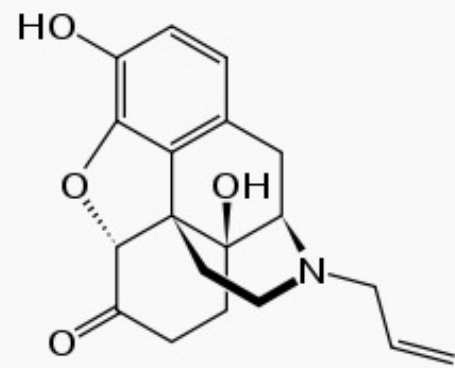
Recently the pharmacological effects of the N-allyl derivative of a potent narcotic analgesic, oxymorphone† (Numorphan (see Fig. 1), were investigated in animals (Blanchard *et al.*¹³)

Am. J. Med. Sci. 245: 23-30, 1963

Oxymorphone



Naloxone



Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.