The quest for non-abusable opioid analgesics:

"If it were that easy…"
Past attempts,
Past successes and
Future possibilities

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Abuse Resistance Opioid Product Conference
Boston
October 27-28, 2005

A special thanks to Don Jasinski for sharing his insights and experiences

Lower Abuse Potential--Strategies

- **Inhibit subjective feelings**

- **Physical characteristics that prevent/retard abuse**

Lower Abuse Potential Strategies

- **Inherent dual mechanism analgesics**
  - ***Analgesic at therapeutic doses***
  - ***Unpleasant effects at higher than therapeutic doses***
  - ***Problem***
    - ***"therapeutic ratio"***

Lower Abuse Potential Strategies

- **Antagonist combination products**
  - *An oral formulation of an opioid with an orally inactive, but parenterally active opioid antagonist.*
  - *Approaches include tamper resistance and sequestered antagonist components.*

Lower Abuse Potential Strategies

- **Aversive combination products**
  - *Contains a new component introduced into a formulation such that the combination product is associated with aversive characteristics.*
  - *Prevent both abuse and overdose when the combination is used in an abusive manner.*

Lower Abuse Potential Strategies

- **A prodrug that is inactive as the parent entity**
  - ***When metabolized by the body is transformed to an active metabolite, hopefully at a metabolic rate that is associated with a lower abuse potential than if the active metabolite itself was directly administered.***

Lower Abuse Potential Strategies

- **"Non-injectable" formulation delivery systems such as dosage forms that become "gummy" when dissolved in water or other solvents**
  - ***Making the active ingredient in the formulation less extractable or not amenable to being injected.***
  - ***Oral dosage forms that create a barrier to being easily extracted for parenteral administration of the active ingredient.***

Lower Abuse Potential Strategies

- **Physically impenetrable products**
  - ***Newer formulation technology which prevents an abuser from gaining access to the Active Pharmaceutical Ingredient (API) for injection or other routes of abuse.***

Lower Abuse Potential Strategies

- **Devices with patient recognition capabilities**
  - ***Dispense medication only to the target patient.***

Lower Abuse Potential Strategies

- **Depot formulations**
  - *Slow onset and sustained release over long periods.*

Lower Abuse Potential Strategies

- **Transdermal systems**
  - *Produce slow and sustained drug delivery.*

Lower Abuse Potential--Strategies

- **Inhibit subjective feelings**
- **Physical characteristics that prevent/retard abuse**

Lower Abuse Potential Strategies

- **Inhibit subjective feelings**
  - **Less euphoria**
  - **Less dependence producing properties**
  - **Inherently unpleasant at higher than therapeutic analgesic doses**
  - **Incorporates an opioid antagonist to create unpleasantness when abused**

Less euphoria

- **Attempts to identify an opioid analgesic with inherently <u>less euphoria</u> (drug liking) at doses higher than therapeutic analgesic doses**
  - **Codeine being less abusable lead to rationale that a better morphine could be identified (1920-30s)**

No. 6,124,282

Drug formulations

September 26, 2000

- **Abstract**
  - Various ***<u>compounds that can inhibit the enzyme CYP2D6</u>*** are disclosed. The compounds are useful in increasing the effectiveness and reducing the abuse potential of drugs that are metabolised by CYP2D6.
- **Inventors**
  - **Sellers; Edward M.** (Toronto, Ontario, CA); **Tyndale; Rachel F.** (Toronto, Ont, CA) Appl. No.: **083027**Filed: **May 22, 1998**

Less dependence producing properties

- How big a difference in the analgesic dose vs. the dependence producing dose would be needed?
- Slower onset of activity
  - Slow absorption
  - Inactive prodrug
  - Mu receptor subtypes

- **Neuroscience. 2005;133(1):209-20.**

  Identification and characterization of six new alternatively spliced variants of the human mu opioid receptor gene, Oprm.

  Pan L, Xu J, Yu R, Xu MM, Pan YX, Pasternak GW.

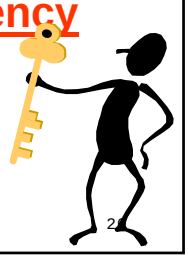
  Laboratory of Molecular Neuropharmacology, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, USA.

Identification and characterization of six new alternatively spliced variants of the human mu opioid receptor gene, Oprm.

- Receptor binding and a wide range of pharmacological studies have proposed several mu receptor subtypes, but only one mu opioid receptor (Oprm) gene has been isolated.
- …we have identified and characterized six new splice variants from the human Oprm gene using a reverse transcription-polymerase chain reaction strategy, yielding a total of 10 human splice variants of the mu opioid receptor MOR-1.

Identification and characterization of six new alternatively spliced variants of the human mu opioid receptor gene, Oprm.

- The dissociation between binding affinity, potency and efficacy for the opioids among these variants may provide insights into the wide range of opioid responses among these agents observed clinically and opens new avenues in designing selective drugs based upon their efficacy and potency rather simple binding affinity.



Inherently unpleasant at higher then therapeutic analgesic doses

- Nalorphine—Merck, first narcotic mu antagonist; also a kappa agonist
  - *No one took a second dose*
  - Antidote for morphine poisoning
- Cyclazocine kappa agonist, mu antagonist good analgesic—orally effective, long lasting
  - *Side-effect profile too close to therapeutic dose*
- Pentazocine

Attempts to identify an opiate analgesic that incorporates an opiate antagonist to create unpleasantness when abused

- Past
  - Failed attempts
- Pentazocine-naloxone
- Buprenorphine-naloxone
- Current
  - "Sequestered" antagonist
  - Naltrexone

No. 4,457,933

Prevention of analgesic abuse

July 3, 1984

- **Abstract**
  - This invention concerns a method for decreasing both the oral and parenteral abuse potential of strong analgetic agents such as oxycodone, propoxyphene and pentazocine by ***combining an analgesic dose of the analgetic agents with naloxone*** in specific, relatively narrow ranges. Oxycodone-naloxone compositions having a ratio of 2.5-5:1 parts by weight and pentazocine-naloxone compositions having a ratio of 16-50:1 parts by weight are preferred.
- **Inventors**
  - **Gordon; Maxwell** (Syracuse, NY); **Pachter; Irwin J.** (Fayetteville, NY) **Assignee: Bristol-Myers Company (New York, NY) Appl. No.: 329839 Filed: December 11, 1981**

No. 6,228,863 & No. 6,627,635

Method of preventing abuse of opioid dosage forms

May 8, 2001 and September 30, 2003

- **Abstract**
  - The invention relates in part to a method of reducing the abuse potential of an oral dosage form of an opioid analgesic, wherein an analgesically effective amount of an orally active opioid agonist is combined with ***an opioid antagonist into an oral dosage form which would require at least a two-step extraction process to be separated from the opioid agonist,*** the amount of opioid antagonist including being sufficient to counteract opioid effects if extracted together with the opioid agonist and administered parenterally.

No. 6,228,863 & No. 6,627,635

Method of preventing abuse of opioid dosage forms

May 8, 2001 and September 30, 2003

- **Abstract**
  - ... ***opioid antagonist into an oral dosage form which would require at least a two-step extraction process to be separated from the opioid agonist,…***
- **Inventors**
  - **Palermo; Philip J. (Bethel, CT); Colucci; Robert D. (Newtown, CT); Kaiko; Robert F. (Weston, CT)**
- **Assignee** Euro-Celtique S.A. (Luxembourg, LU)
- **Filed** December 22, 1998

No. 6,696,088

Tamper-resistant oral opioid agonist formulations

February 24, 2004

- **Abstract**
  - Disclosed is an oral dosage form comprising ***(i) an opioid agonist in releasable form and (ii) a sequestered opioid antagonist which is substantially not released when the dosage form is administered intact,*** such that the ratio of the amount of antagonist released from said dosage form after *tampering* to the amount of said antagonist released from said intact dosage form is about 4:1 or greater, based on the in-vitro dissolution at 1 hour of said dosage form in 900 ml of Simulated Gastric Fluid using a USP Type II (paddle) apparatus at 75 rpm at 37 degrees C. wherein said agonist and antagonist are interdispersed and are not isolated from each other in two distinct layers.

No. ***6,696,088***

Tamper-resistant oral opioid agonist formulations

February 24, 2004

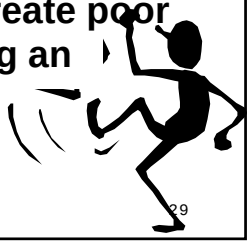
- . **Inventors**
  - **Oshlack; Benjamin (New York, NY); Wright; Curtis (Nowalk, CT); Haddox; J. David (Upper Stepney, CT)**

Lower Abuse Potential Strategies

- **Inhibit subjective feelings**
- **Physical characteristics that prevent/retard abuse**

Lower Abuse Potential Strategies

- **Physical characteristics that prevent/retard abuse**
  - **Inherently poor physical properties for preparing an injectable solution**
  - **Attempts to identify an opioid analgesic with modified formulations to create poor physical properties for preparing an injectable solution**



Attempts to identify an opiate analgesic with inherently poor physical properties for preparing an injectable solution

- **Poor aqueous solubility**
  - **Codeine**
  - **Imodium**
- **Poor aqueous solubility (quaternary ammonium salt)**
  - **Grind up and inject and get morphine like effects**
- **Endo with oxycodone, oxymorphone, nalbuphine**
  - **Poor bioavailability with 1st pass, now injectable**

No. 4,070,494

Enteral pharmaceutical compositions

January 24, 1978

- **Abstract**
  - Enteral pharmaceutical compositions containing medicinal agents having parenteral abuse potential are rendered resistant to aqueous extraction through the incorporation of a sufficient amount of a nontoxic, water gelable material. Attempts to extract the medicinal agent for parenteral abuse are thus inhibited or prevented ***since the material gels in the presence of water*** leaving no filterable liquid.
- **Inventors**
  - **Hoffmeister; Friedrich (Wuppertal, DT); Hiltmann; Rudolf (Wuppertal, DT); Wollweber; Hartmund (Wuppertal, DT); Kramer; Helmut (Leverkusen, DT)**
- **Assignee**: **Bayer Aktiengesellschaft** (DT)

No. 5,149,538

Misuse-resistive transdermal opioid dosage form

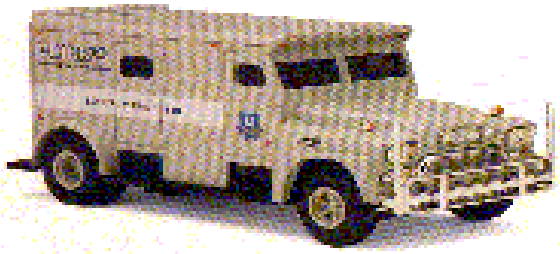
September 22, 1992

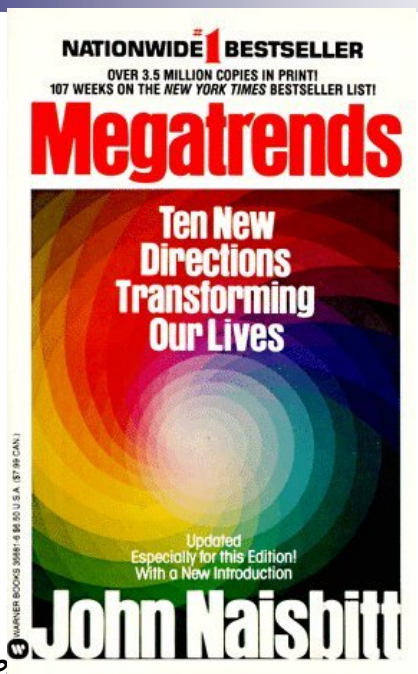
- **Abstract**
  - A misuse-resistive dosage form for the transdermal delivery of opioid comprises, in combination, 1) one or more opioid permeable to the skin, 2) delivery means permeable to said opioid, 3) one or more antagonist for said opioid releasable upon ingestion or solvent immersion, and 4) impermeable barrier means separating said opioid and said antagonist. .
- **Inventors**
  - Granger; Colin D. (Chester, NJ); Simon; Thomas H. (Morris Plains, NJ)
- **Assignee** Warner-Lambert Company (Morris Plains, NY)

CPDD Formulations Workshop
April 19-20, 2005, Bethesda, MD

A New Technology to Increase the Mechanical Stability of Matrix Tablets to Prevent Abuse by Crushing or Chewing

Judy B. Ashworth, M.D.
International Project Manager
Grunenthal GmbH





PTO Search Results
Hits "in the patent" (1976 to 6/14/05)

- analgesic 13,052
- analgesic AND prevention 3,094
- prevention AND abuse 1,836
  - prevent AND abuse 2
- analgesic AND abuse 870
- opioid AND abuse 625
  - opiate AND abuse = 625
- reduced abuse AND opiate 2
- reduced abuse AND opioid 1

PTO Search Results
Hits "in the Title" (1976 to 6/14/05)

- abuse 105
- prevention AND abuse 5
  - prevent AND abuse 0
- opioid AND dosage form 3
- opioid AND abuse 3
- opiate AND abuse 0
- abuse AND analgesic 1

PTO Search Results

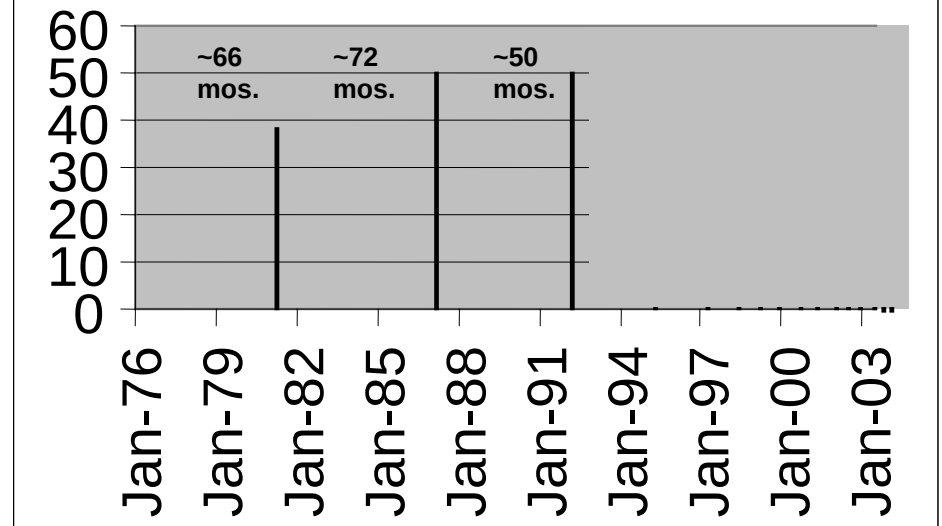
Hits "in the Title" (1976 to 6/14/05)

- prevent abuse 0
- reduce abuse 0
- reduce AND abuse 0
- prevent AND abuse 0
  - 5 for prevention AND abuse

Metric for Trends--US Patents?

- Patent search from 1976 to June 2005
- Search for "analgesic" and "abuse" in the patent
- 870 Issued US Patents

Time Required for Each 50 US Patents with "Analgesic" and "Abuse" in the Patent



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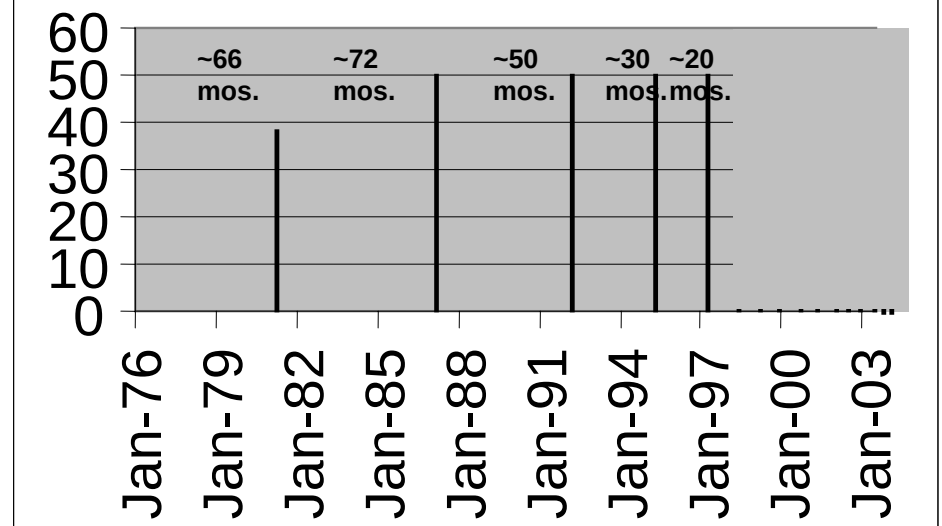

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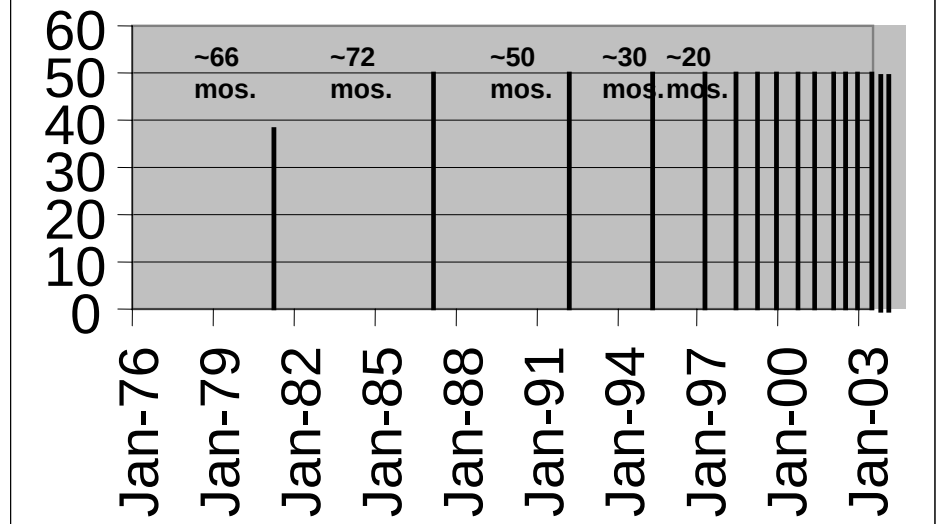

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"If it were that easy…"

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If it were that easy…

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  - **Less euphoria**
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- **Physical characteristics**
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