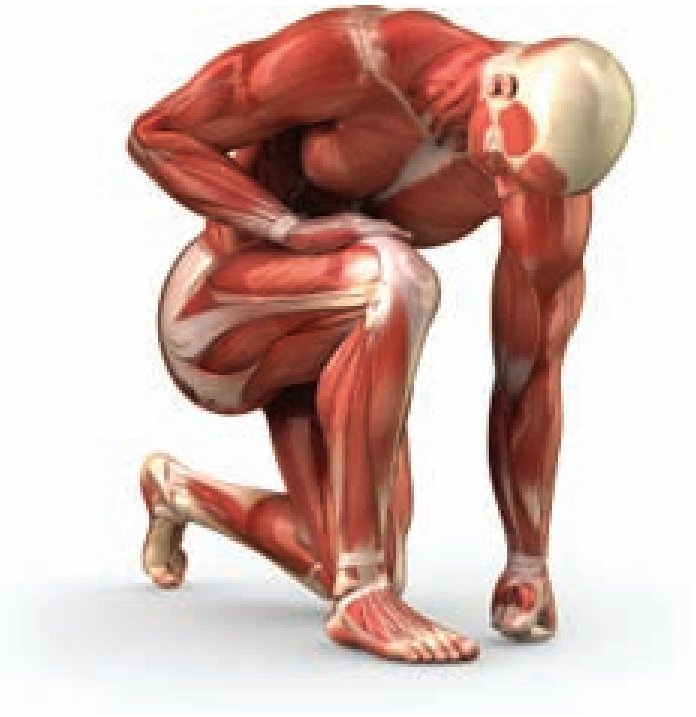
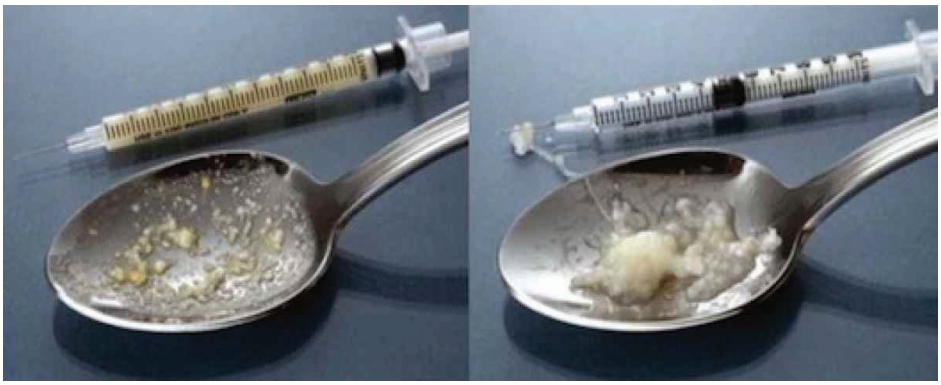
THERAPEUTIC CLASS OVERVIEW

Moderate to Severe Pain: Novel Abuse Deterrent Formulation Technologies and Emergence of Novel Mechanisms in the Management of Pain





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f. Topical clonidine gel
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j. DWP05195

7. FDA Perspective on Abuse deterrent formulations (Opioids) Companies mentioned:

- AbbVie
- AcelRx
- Acorda Therapeutics
- Actavis
- Acura Pharma
- Altus formulations
- Amorsa Therapeutics
- AstraZeneca
- BioDelivery Sciences International Inc
- Cara Therapeutics
- Catalent
- Charleston
- Collegium Pharma
- Convergence
- Daiichi
- Daewoong

- Depomed
- Durect
- Egalet
- Eli Lilly
- Elite Pharma
- Endo
- Flamel Technologies
- Flexion Therapeutics
- Glenmark
- Grunenthal
- Immune Pharmaceuticals
- Impax Pharmaceuticals
- Inspirion Delivery technologies
- Intelli Pharmaceutics
- Johnson and Johnson
- KemPharm
- Kineta
- Kunwha Pharmaceutical
- Medallion Therapeutics
- Nektar
- Orbis Biosciences
- Orexo
- Pain Therapeutics
- Pfizer
- Purdue
- Recro
- Relmada Therapeutics
- Signature Therapeutics
- Spinifex pharma

Introduction

Pain is the leading cause of disability in the US, affecting more than cancer, diabetes and heart disease combined. Current analgesics for persistent pain are relatively ineffective, are associated with significant adverse effects or abuse liability, and do not reduce pain in all treated individuals. Opioids (e.g. , morphine, codeine, oxycodone) are currently one of the most potent groups of analgesics used clinically, with prescriptions increasing by 50% over the past 10 years for chronic, non-cancer pain. However, there is clear evidence that as opioid prescription rate rise, there is a corresponding increase in opioid overdose deaths, misuse and addiction. These adverse effects are attributed to the opioid agonist effects on central opioid receptors—causing dependence, tolerance, sedation, and respiratory depression.

Non-steroidal and steroidal anti-inflammatory drugs have serious side effects such as gastric erosions, ulcer formation, bleeding, hypersensitivity reactions, cardiovascular toxicity, renal toxicity, and hepatotoxicity. In addition, they are also not peripherally selective thereby causing a range of central adverse effects. Over the past 20 years, most analgesic development activities have been limited to the reformulation of opioids, production of new cyclooxygenase (COX) inhibitors, amine reuptake inhibitors and anticonvulsants, and introduction of topical local anesthetics—all of these act on well-established targets. A significant unmet need exists in the emergence of novel mechanism which will avoid the current NSAIDS side effects with improved efficacy. Several newer mechanisms currently being explored will have the ability to replace opioids in the treatment of acute and chronic moderate to severe pain.

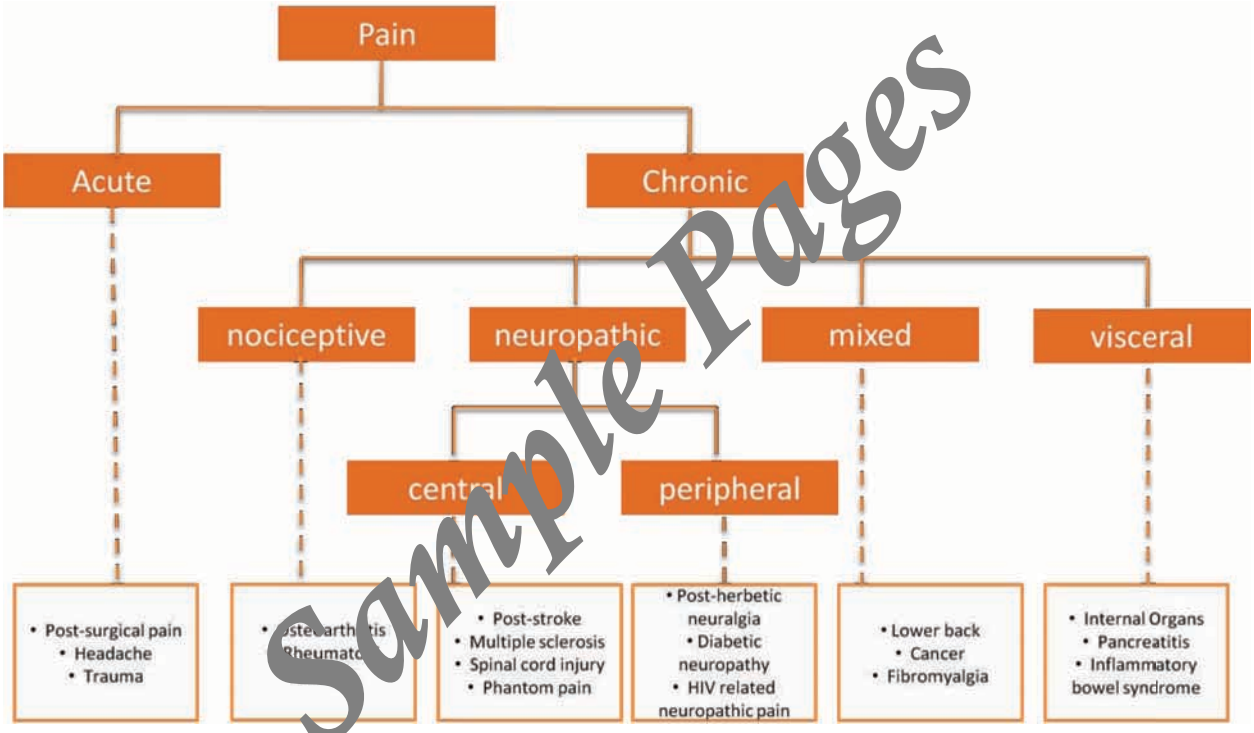
Globally, pain is one of the important therapy areas with a market size of over $50b in 2013, and is expected to grow at 10%. The recent patent expiry of Cymbalta and Lyrica (2018) will have significant impact on the overall pain market size in the near future. However, several pipeline molecules are emerging to fill this gap. The importance of abuse deterrent labeling in the formulations can be better understood from FDA's non-approval of oxycontin generics in 2013. The revised labeling with abuse deterrence has protected Purdue's oxycontin revenue slide from its generization.

In the wake of abusive potential of opioids drugs reported all across the US, FDA recently drafted guid-

ance for evaluation and labeling of opioids formulations based on their ability to reduce its abusive potential (tier 1 to 4). Despite the process being in nascent stage, several specialty companies have future. In this report, we have discussed a number of novel delivery technologies employed in the formulation of abuse deterrent product, technologies employed in enhancing patient compliances and emerging novel mechanisms in the management of pain.

Chart: 1

CLASSIFICATION OF PAIN



Source: MP Advisors, Company Report

What is Pain: Pain is defined by the International Association for the Study of Pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage".

Pain can appear in many forms; for example, it can be pulsing, aching, sharp, dull or even drilling. Understanding how pain manifests is crucial for its treatment, since the symptoms that a patient experiences provide clues about the cause and origin of the pain. Pain is a very personal and subjective experience. There is no test that can measure and locate pain with precision. Pain can be classified as noci-

NEUROPATHIC PAIN MARKET

Neuropathic pain is a chronic pain condition caused by a primary lesion or dysfunction in the nervous system. It can be a consequence of many different insults, such as trauma, neuronal injury or infection. The most commonly studied neuropathic pain subtypes include diabetic neuropathic pain (DNP), postherpetic neuralgia (PHN) and HIV-related neuropathic pain. Collectively, these three conditions were estimated to affect over 6m people across the seven major pharmaceutical markets (the United States, Japan, France, Germany, Italy, Spain and the United Kingdom) in 2010.

Today, medicines that act by blocking sodium or calcium channels such as the gabapentinoids and other

is advancing age. Other possible risk factors for PHN include severity of acute herpes zoster pain, extent of rash, and duration of prodromal pain. The incident cases of PHN in the 7 major markets were 241,808 patients in 2012 and growing at 20% each year.

About Diabetic peripheral neuropathy (DPN): Diabetic neuropathy is clinically defined as "the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of

Table: 2
CLASSIFICATION BASED ON INTENSITY OF PAIN

	Brands	Generic	2013 sales ($m)	Company
Severe	BuTrans	Buprenorphine transdermal patch	$134	Purdue pharma
	Kadian	Morphine XR capsules	$264	Actavis
	Avinza	Morphine XR capsules		Pfizer
	Opana ER	Oxymorphone tablets		Endo
	Nucynta	Tapentadol ER tablets		
	Oxycontin	Oxycontin		Purdue pharma
Moderate	Vicodin	Hydrocodone/Acetaminophe tablets		AbbVie
	Percocet	Oxycodone/Acetaminophen		Endo
				Valeant/JNJ
				Pfizer
				Eli Lilly
	Gralise/neurontin/Horizont	Gabapentin tablets		Depomed/Xenoport
Mild	Lidoderm	Lidocaine patch 5%		Teikoku/Endo

Source: MP Advisors, Company Report

Table 3
MARKETED FENTANYL DOSAGE FORMS (US): TRANSDERMAL PATCHES, BUCCAL AND SUBLINGUAL TABLETS AND FILMS FOR PAIN RELIEF

Brand name	Dosage forms	Company	FDA Approval	REMS Status	Therapy Equivalent
Abstral	Sublingual tablet (0.1-0.8mg)	Galena Biopharma	Jan-11	REMS	No
Actiq	Troche/Lozenge (transmucosal)	Cephalon		REMS	AB
Duragesic	Transdermal film	JNJ		REMS	AB
Fentora	Buccal and sublingual tablets (0.1-0.6mg)	Cephalon		REMS	No
Innovar	Fentanyl+Droperidol Injection	Akorn			
Ionsys	Transdermal iontophoresis	Incline Therap			
Lazanda	Metered nasal spray	Depomed		REMS	No
Onsolis	Buccal film (0.2-1.2mg)	Meda Pharma		Discontinued	No
Sublimaze preservative free	Injection 0.05mg/ml	Akorn		No	AB
Lazanda	Nasal spray	Depomed		REMS	No
Subsys	Sublingual spray	Insys Therap		REMS	No
Sufenta preservative free	Injection	Akorn		No	AB

Source: MP Advisors, Company Report

Oxycodone DETERx® would potentially be the only abuse-deterrent, ER opioid that could be administered as a sprinkle directly into the mouth or onto soft food, and could also be administered through an enteral feeding tube.

Pipeline using DETERx technology

COL-003 (Oxycodone) –PhIII completed and expected to be filed in 2014. Collegium has also completed an extensive program of abuse-deterrent studies that follow FDA's "Abuse-Deterrent Opioids – Evaluation and Labeling" draft guidance published in January 2013.

COL-172 (Oxymorphone)-IND filed

PODRAS Platform technology (Paradoxical OverDose Resistance Activating System)

-Intellipharmaceutics

It is designed to prevent overdose when more pills than prescribed are swallowed intact. It is designed to deter abuse by both physical interference and overdose. Preclinical studies suggests that, if more tablets than prescribed are deliberately or inadvertently swallowed, the amount of drug active released over 24h may be substantially less than expected, even possibly approaching zero. However, if the prescribed number of pills is swallowed, the drug release should be as expected.

Ex. Rexista (Oxycodone XR tablets) planned for clinical trials

IntelliPaste Technology (Intellipharmaceutics)

The IntelliPaste™ technology is comprised of blends of multiple polymers, oils, excipients and drug active(s) which result in a paste-in-a-capsule dosage form. The physical attributes of the paste include that it is thixotropic, pseudo plastic and non-Newtonian or, in layman's terms, like toothpaste. Typically, it is formulated as having very low solubility in water or oil, and low solubility in alcohol. These characteristics enable the resulting drug product to have tamper-deterrent properties, and to resist dissolution in even high concentrations of alcohol. As a result, IntelliPaste™ is the Company's preferred delivery technology for the controlled delivery of opiates, narcotics and other central nervous system ("CNS") drug products which are susceptible to unlawful diversion or abuse.

nPODDDS (Intellipharmaceutics)

endpoint demonstrating significantly (p<0 005) improved chronic pain relief compared to placebo. In July 2014, positive topline results (p<0.0001) were reported from the PhIII efficacy study in opioid experienced subjects (BUP-307).

OptiGel Lock Technology (Catalent Pharma)

The OptiGel Lock™ technology limits abuse of the dose form by incorporating multistage levels of deterrence technology, preventing the manipulation of the product into an inhalable or injectable form, and rendering the recovered product unusable for further manipulation. In addition, the Softgel dose form cannot be grounded, blended, or crushed to create powder or microparticle form. OptiGel Lock™ technology therefore offers effective deterrence, preventing many common methods of abuse.

Intrathecal Drug Delivery System (Medallion Therapeutics, Ph II, morphine implantable pump)

Using this implantable pump system, patients can control the drug delivery depending on its analgesia effects. Medallion Therapeuticas is exploring the device in PhII study and the final data is expected in YE 2015.

Nobuse Technology (Tris Pharma)

Nobuse™ is an innovative and patent pending technology utilized in the formulation of drugs with abuse potential. The abuse deterrence is attained by physical means and works at two levels: the technology forms a complex of a drug with very fine polymeric particles; then coating the drug-polymer complex with a highly flexible non-breakable coating. This makes the product resistant to prevalent drug extraction approaches used on conventional formulations, without the need of additional ingredients. The products based on Nobuse technology can be formulated in any oral dosage forms, such as tablets, liquid suspensions, oral dissolving tablets (ODT), and films or strips in either immediate release or 12 to 24 controlled release profiles.

Egalet Delivery System (Egalet)

Egalet created two distinct drug delivery systems, each with novel abuse-deterrent features and the ability to control the release profile of the active pharmaceutical ingredient, or API. It uses an injection

acts peripherally and does not cross the blood-brain barrier, thus highlighting its potential as an effective treatment for severe chronic pain without the risk of addiction, a common side effect of centrally acting opiates. It is FDA approved and currently marketed as Prialt®.

Angiotension II antagonist (Spinifex, PhII, neuropathic pain)

It is a novel chronic pain therapeutic, a highly selective AT2 receptor antagonist, and delivered clinical proof of concept in a PhII study. Recognizing the limitations in current treatments for neuropathic pain, EMA401 is being developed as a potential first-in-class oral treatment for neuropathic pain and related symptoms without central nervous system side effects. The initial PhII clinical trial of EMA401 was in patients with postherpetic neuralgia (PHN) and its results have been published in The Lancet.

Multi-day formulation of Tramadol (Orbis Bio, ORB-201, Post surgical pain, Preclinical)

ORB-201 is an injectable, multi-day formulation of Tramadol, a weak μ-opioid receptor agonist, capable of providing baseline, systemic pain relief, thereby reducing the consumption of potent opioids. The primary advantage of this product is the prophylactic establishment of baseline analgesia with a tightly controlled pharmacokinetic profile free of the peak-to-trough variations of immediate-release analgesics that often lead to break-through pain and the need to deliver potent opioids. More specifically, ORB-201 provides a safe and effective multi-day analgesic capable of reducing potent-opioid consumption during the first several days after surgery-induced pain.

Nav1.7 Sodium channel modulator inhibitor

Voltage-gated sodium channels (Navs) are an important family of transmembrane ion channel proteins and Nav drug discovery is an exciting field. Pharmaceutical investment in Navs for pain therapeutics has expanded exponentially due to genetic data such as SCN10A mutations and an improved ability to establish an effective screen sequence, for example, IonWorks Barracuda®, Synchropatch® and Qube®.

Moreover, emerging clinical data (AZD-3161, XEN402, CNV1014802, PF-05089771, PF-04531083) combined with recent breakthroughs in Nav structural biology pave the way for a future of fruitful prospective Nav drug discovery.