DETERRENTS TO NARCOTIC ABUSE: A REVIEW OF MECHANISMS AND CLINICAL APPLICATION

Patrick Cogan, Pharm.D. Candidate

Narcotic analgesics provide effective pain relief for patients who cannot adequately control their pain with or have contraindications to other pain medications. The problem with these agents lies in the great potential and ease of abuse.

Prescription drug abuse has been fueled by the large number of "pill mills," especially in the state of Florida. A Prescription Drug Monitoring Program (PDMP) in Florida was launched in 2011 to attempt to reduce overprescribing of controlled medications.[1] Florida pharmacies and doctors sold over 622 million doses of oxycodone in 2010.[1] After the PDMP was launched, this number was reduced to 498 million doses sold in 2011. Prescription drug abuse contributed to more than 1,268 deaths in Florida in 2010 and 1,175 in 2011.[2] The attempt to limit the prescribing of controlled medications has had some impact, but the addictiveness of these drugs and their abuse potential remain strong.

Popular methods of abusing these agents include crushing tablets for faster absorption, intranasally "snorting" powder from crushed tablets, smoking tablets via inhaling vaporized particles, and intravenously injecting the extracted drug dissolved in water. These methods of quickly introducing the drug into the blood stream result in very fast and high peak concentrations, corresponding to increased risk of addiction. Popularity of abusing prescription drugs has been on the rise since 1990, creating a stigma surrounding the prescribing and dispensing of these medications. In 2008 there were nearly 15,000 deaths due to overdose of prescription analgesics, a large increase from the 4,000 deaths in 1999.[3] Additionally, prescription drug abuse accounted for nearly 500,000 emergency department visits in 2009, costing health insurers approximately $72.5 billion per year. According to the Drug Abuse Warning Network (DAWN) in 2010, 12 million people reported using prescription medications without a prescription or misusing their prescription to get a euphoric effect.[4] The National Survey on Drug Use and Health showed how widely abused narcotic pain relievers are among persons aged 12 years or older: in 2009, these medications were the most commonly abused drugs next to marijuana.[5]

Due to the rise in abuse of these drugs, many pharmaceutical companies have begun investigating different formulations that provide pain relief to those patients who need it, while simultaneously minimizing abuse potential. This article will explore these agents and formulations along with a discussion of the clinical impact and relevance of these medications in today's health care model.

PHARMACOLOGY OF NARCOTICS

The pharmacologic actions of opioids are mediated by mu, kappa, and delta opioid receptors (**Table 1**). Most opioid analgesics achieve their analgesic activity from

---

INSIDE THIS ISSUE:

DETERRENTS TO NARCOTIC ABUSE: A REVIEW OF MECHANISMS AND CLINICAL APPLICATION

action at mu opioid receptors. However, these are also the receptors which stimulate physical dependence. Antagonists to opioid receptors include naloxone, naltrexone, nalbuphine (mixed agonist/antagonist), and buprenorphine (mixed agonist/antagonist). Many of the actions of these opioid receptors are suppressed as tolerance to agonists increases. Mechanisms of tolerance, such as receptor down-regulation, contribute to addiction and abuse associated with the need for higher doses to feel the same "high."[6-9]

MECHANISMS OF DRUG ABUSE RESISTANCE AND DETERRENCE

With the rise in narcotic abuse pharmaceutical companies have developed novel formulations and combinations of prescription narcotics in an attempt to reduce abuse of these medications. However, to date the FDA has not approved any language on labels that include drug abuse prevention for these novel medication forumulations.

Abuse resistant formulations attempt to prevent abuse by minimizing the chance that a significant portion of active ingredient can be extracted through physical or chemical manipulation of the product.[10] Extended-, controlled-, and sustained-release dosage forms prevent rapid absorption of medications when taken whole, but do not necessarily prevent forms of abuse involving crushing tablets or extracting capsules. Formulations that employ physical barriers are designed to prevent abuse by preventing or limiting extraction of the active ingredient. A subset of the physical barrier method includes crush resistant formulations that specifically prevent a tablet from being crushed into a fine powder and thus limit extraction. Prodrugs require the medication be ingested and enzymatically converted to the active form hepatically, however this idea has yet to be incorporated in an FDA approved medication.

Abuse deterrent formulations (ADFs) attempt to reduce abuse by adding a second drug that has undesirable effects when taken in excess. ADFs are designed to reduce abuse without affecting analgesia

when compared to the original drug.[11,12] Combinations of opioid receptor agonists and antagonists prevent abuse by releasing the sequestered antagonist when the original dosage form is crushed or dissolved. Combinations allow for normal absorption of the active agent when taken orally as prescribed. The release of the antagonist causes withdrawal effects in the abuser, decreasing the desirability of the medication for abuse. Another abuse deterrent formulation proposed is a combination of an opioid with niacin, with the intent to cause intense flushing when taken in excess.

FDA APPROVED ABUSE RESISTANT NARCOTICS

There are no narcotics approved by the FDA based on claims of reducing abuse. However, there are products approved with various formulations to aid in preventing abuse (**Table 2**).

Suboxone® (buprenorphine 2 mg and 8 mg, naloxone 0.5 mg and 2 mg) was approved for opioid dependence and withdrawal in 2002.[13] The inclusion of naloxone to buprenorphine at a 1:4 ratio allows for the medication to be effective when taken orally, but causes withdrawal symptoms when injected by patients with previous opioid tolerance.[14] Naloxone undergoes extensive hepatic first-pass metabolism resulting in minimal systemic absorption when taken orally.[15] Suboxone®, however, is still able to produce an opioid agonist "high" without withdrawal symptoms when injected by non-dependent or opioid-naive patients, resulting in some debate of the effectiveness of naloxone in blunting the opioid agonist effects (e.g. euphoria).[16]

Talwin NX® (pentazocine 50 mg, naloxone 0.5 mg) is another example of a combination agonist/antagonist formulation. Due to increased abuse of Talwin® and tripelennamine through intravenous injection, Talwin NX®, a combination of 50 mg pentazocine and 0.5 mg naloxone, was approved for moderate and severe pain in 1982 and Talwin® was subsequently discontinued. Based on DAWN reports of pentazocine abuse, events were reduced by 70% – 71% in the two years after Talwin NX® was approved.[17]

Table 1 | Opioid Receptor Effects

Opioid Receptor Type	Receptor Mediated Actions	Actions Reduced with Tolerance
Mu (μ)	analgesia, respiratory depression, euphoria, miosis, sedation, muscular rigidity, nausea, constipation, physical dependence	analgesia, respiratory depression, euphoria, sedation, nausea
Kappa (κ)	analgesia, dysphoria, miosis, sedation, muscular rigidity	analgesia, dysphoria, sedation
Delta (δ)	analgesia, muscular rigidity	analgesia

Table 2 | Abuse Resistant and Deterrent Narcotics

Drug (Brand Name)	Dose/Frequency	Abuse Resistant or Deterrent Features	FDA Status	Cost (30 count)*
Buprenorphine/naloxone (Suboxone®)	2 mg/0.5 mg 8 mg/2 mg QD	Combination agonist/antagonist	Approved	Tabs: $182.99 $310.99 Film: $149.99 $233.99
Pentazocine/naloxone (Talwin NX®)	50 mg/0.5 mg Q3-4h	Combination agonist/antagonist	Approved	Generic: $23.99
Extended-release morphine/ naltrexone (Embeda®)	20 mg – 100 mg/ 0.8 mg – 4 mg Q12-24h	Combination agonist/antagonist	Approved	$157.99 - $535.99
Extended-release tramadol (Ultram ER®)	100 mg, 200 mg, 300 mg QD	Crush resistant	Approved	$169.99 $264.99 $367.99
Extended-release oxycodone (Oxycontin®)	10 mg – 80 mg Q12h	Crush resistant	Approved	$83.59 – $535.99
Extended-release hydromorphone (Exalgo®)	8 mg, 12mg, 16 mg QD	Crush resistant	Approved	$326.99 $488.99 $649.99
Oxycodone (Oxecta®)	5 mg, 7.5 mg Q4-6h	Crush resistant, nasal irritation, gel-forming	Approved	$110.99 $110.99
Extended-release oxycodone (Remoxy®)	5 mg – 40 mg Q12h	Water insoluble, crush resistant	Complete Response Letter	N/A
Oxycodone/niacin (Acurox®)	5 mg/30 mg 7.5 mg/30 mg Q6h	Unpleasant effects, crush resistant, nasal irritation, gel-forming	Rejected, switched to Oxecta	N/A
Controlled-release oxycodone (Rexista®)	40 mg QD	Crush resistant, reduced absorption with alcohol	Proposed, no NDA submitted	N/A
Extended-release oxycodone/ naltrexone (Oxynal®)	N/A	Combination agonist/antagonist	NDA, status undetermined	N/A
Oxycodone/ultra-low-dose naltrexone (Oxytrex®)	N/A	Combination agonist/antagonist	NDA, status undetermined	N/A

N/A – Not available; NDA – New Drug Application; Q12h – every 12 hours; QD – once daily
*Prices represent cash prices obtained from a Central Florida chain pharmacy

Embeda® (extended-release morphine sulfate 20 mg – 100mg, naltrexone 0.8 mg – 4 mg) was approved for moderate to severe pain in 2009. Embeda® capsules contain small pellets of morphine sulfate embedded with naltrexone.[18] When swallowed whole, the medication relieves pain without any effects from the naltrexone. However, when chewed or crushed, naltrexone is released, blocking of the effects of morphine and causing subsequent unwanted negative ef-

fects. Safety reports have confirmed Embeda® to be comparable to extended release morphine with 25 reports of opioid withdrawal symptoms reported.[19] Most reports are attributable to capsule tampering or history of substance abuse. Further studies regarding the clinical significance of naltrexone released upon tampering are required to be able to interpret the effectiveness of this formulation in deterring abuse.

Some extended release formulations incorporate

physical barriers and crush resistant formulations in an attempt to prevent tampering of the agent for intravenous injection. Ultram ER® (extended-release tramadol 100 mg – 300 mg), Exalgo® (extended-release hydromorphone 8 mg – 16 mg), and OxyContin® (controlled-release oxycodone 10 mg – 80 mg) are all approved narcotic agents that incorporate crush resistance to prevent tampering.[20-22] The claims of abuse resistance are not endorsed by the FDA and studies have yet to be performed to confirm the effectiveness of these abuse-prevention formulations.

Oxecta® (immediate-release oxycodone) was approved for moderate to severe pain in 2011. Originally investigated under the name Acurox® (oxycodone and niacin), Oxecta® removed the niacin portion and focused on physical resistance to abuse without affecting effectiveness.[23] Utilizing patented Aversion Technology, the tablet is designed to break into larger clumps instead of fine powder when crushed to prevent abuse. If inhalation is attempted, the product will cause irritation.[24] Additionally, the product is formulated to form a thick gel when combined with water to prevent intravenous abuse. To date, there has yet to be an established study linking the new formulation of Oxecta® to a lower abuse liability compared to immediate-release oxycodone.[25]

NOVEL ABUSE RESISTANT NARCOTICS UNDER REVIEW

Pharmaceutical companies have begun investigating different formulations to reduce abuse liability. Because it is difficult to organize a controlled clinical trial to assess reduced abuse, no product has yet gained approval for this purpose. The following products are currently in New Drug Application (NDA) status or have received a Complete Response Letter (CRL) from the FDA (meaning the drug has been rejected by the FDA in its present form).

Remoxy® (extended-release oxycodone 5 mg – 40 mg) is a water insoluble, highly viscous formulation of oxycodone, utilizing Aversion Technology similar to Oxecta. A CRL from the FDA was received in June 2011. A Phase I trial conducted compared chewed and whole Remoxy® under fed conditions to oxycodone IR and crushed oxycodone ER under fasting conditions.[26] The study concluded there was some promise for reduced abuse potential. Because the comparison groups did not have the same conditions however, the results for the study do not reliably translate into real-world abuse potential.

Acurox® (oxycodone 5 mg – 7.5 mg and niacin 30 mg) was the precursor to the now approved Oxecta®. The niacin in the formulation added a new dimension

to the abuse deterrence by utilizing the undesirable flushing effect when taken in large doses. This will prevent abuse not only from intravenous and intranasal use, but also from oral use. The NDA was rejected by the FDA in April 2010 due to lack of evidence of niacin being a strong enough deterrent to prevent abuse, eventually leading to the removal of niacin and approval of Oxecta®.[27]

Rexista® (controlled-release oxycodone) is a proposed product with once daily (QD) dosing and claims that it will prevent crushing and injecting. The capsule is formulated with a paste inside in attempt to deter abuse through snorting, inhalation, or injection.[28] The product also claims the ability to resist release of the active ingredient when taken simultaneously with alcohol, though an explanation for this mechanism is not yet available. There has been no NDA submitted for this product.

Oxynal® (extended-release oxycodone and naltrexone) and Oxytrex® (oxycodone and ultra-low-dose naltrexone) are two additional products that have submitted NDAs, but the current status of their development is unclear. Both products utilize agonist/antagonist combinations to deter abuse when the product is crushed or injected.

Several patents have been filed with plans to investigate prodrugs as a means of reducing abuse liability. No NDAs have been submitted to investigate the impact of prodrugs on abuse of narcotics. One example, NRP-290, is currently in Phase I/II trials.[29] It is a lysine-modified opioid prodrug that requires enzymatic cleavage within the gastrointestinal tract. This causes the drug's effects to be nullified with intranasal or intravenous administration. No published trials are available at this time to support the effectiveness of this formulation.

CLINICAL TRIALS FOR DRUG ABUSE DETERRENT EFFECTIVENESS

There have been few clinical studies evaluating the effectiveness of the products reviewed in this article at reducing abuse potential. Most of the studies have a low number of subjects and lack significance to confirm or deny the effectiveness of different deterrence mechanisms. To establish a method to evaluate the abuse potential of different products a 2006 study designed and validated an Opioid Attractiveness Scale (OAS).[30] The OAS study consisted of 144 subjects and developed a 17-item scale to assess intrinsic (pharmacological effects, methods of abuse, etc.) and extrinsic (availability, cost, etc.) factors of individual drug products. The study demonstrated agreement of

OAS scoring on 14 different medications by groups consisting of opioid abusers and experts in opioid abuse. A study concluded Oxycontin® to have the highest abuse potential of the studied drugs and Duragesic Transdermal® to have the lowest abuse potential. A follow-up study was completed in 2010 with the intent to predict the attractiveness of the not-yet-marketed Remoxy® for abuse as determined by 38 substance abuse counselors.[31] Using the previously validated OAS, Butler et al. concluded Remoxy® to have a lower abuse potential than Oxycontin®, Percocet®, and Vicodin®, but not Talwin NX®.

While many of the products reviewed in this article have traits believed to reduce abuse potential and attractiveness, few studies have been conducted to support these claims. A handful of studies demonstrated how different formulations reduce value and attractiveness of abuse, most of which showed positive results.[32-36] Tomkins et al. showed no difference in abuse liability when comparing oxycodone to oxycodone + ultra-low-dose naltrexone in experienced opioid abusers.[37] Webster et al. studied oxycodone + naltrexone and showed adequate pain control compared to oxycodone alone with significantly reduced side effects of constipation, somnolence, and pruritis.[35]

Of the studies demonstrating abuse liability, some study designs may contribute to a better understanding of how to assess a drug's potential for abuse. In a randomized, double-blind, crossover trial, Stauffer et al. compared the pharmacodynamic effects (including drug-liking and euphoria) of whole and crushed morphine sulfate + sequestered naltrexone (ALO-01) to morphine sulfate solution (MSS) and placebo in non-dependent opioid users.[32] The study found whole and crushed ALO-01 produced lower peak concentration levels and flatter effect-time profiles for subjective measures. ALO-01 caused less pupillary constriction than MSS. The authors concluded that ALO-01 has reduced desirability compared to MSS. Another study using Embeda® found when the capsule was crushed, the naltrexone abated drug liking and euphoria relative to that of an equal dose of immediate-release morphine.[33]

An unpublished study performed on 40 subjects assessed the "drug-liking" response and safety of crushed Oxecta® compared with crushed immediate-release oxycodone tablets inhaled intranasally.[25] The study demonstrated that Oxecta's® mechanism of reducing abuse may reduce "drug-liking," but a definitive conclusion could not be reached.

Lastly, Vosurg et al. took an objective approach to determine abuse potential of crush resistant oxymorphone compared to non-crush resistant oxymorphone in 25 current intravenous prescription opioid abusers.[36] The study measured the particle size of crushed tablets for intranasal inhalation and percent yield in extracts for intravenous abuse in addition to subjective opinions from subjects on desire to abuse the prepared formulations. The investigators found fewer crush resistant than regular particles were smaller than 1.705mm (9.8% vs. 97.7%), the maximum cutoff for the Sympatec Qicpic image analyzer used to analyze particle size. There was no significant difference in percent yield of extracts and a less relative abuse value of the crush resistant tablets. This study shows promise for crush resistant formulations to be effective in preventing abuse

These studies form a good foundation for future study designs to determine the effectiveness of different abuse deterrent technologies, but ultimately epidemiologic studies need to be conducted to determine the true impact these new formulations have on widespread abuse. Without this data, accurate assessment the impact these new formulations have on drug abuse cannot be made.

CLINICAL APPLICATION OF ABUSE RESISTANT AND DETERRENT MEDICATIONS

With increased awareness of alternative formulations for many narcotics, it is important to use good judgment on a case by case basis to determine the appropriateness of these agents. Many screening methods can be used to evaluate an individual patient's opioid abuse potential including the Current Opioid Misuse Measure (COMM),[38] Opioid Risk Tool, Prescription Drug Abuse Questionnaire, and several others. Another useful tool is the Prescription Opioid Documentation and Surveillance (PODS) System, used to identify patients at risk for opioid abuse as well as helping identify patients with comorbidities contributing or related to chronic pain.[39]

After assessing a patient's risk of prescription drug abuse, it is important to take into account the higher costs that may be associated with abuse deterrent formulations. Since most of these formulations are not available generically, drug acquisition cost will be higher.

After starting therapy with a prescribed narcotic, it is important to follow up with the patient and monitor their progress. If a patient is taking more medication than prescribed, there is the possibility of dependence and abuse or the possibility that increased pain levels are requiring dose adjustments. Utilizing the Pain Assessment and Documentation Tool (PADT), a practitioner can assess pain management using the 4 A's (analgesia, activities of daily living, adverse events, and aberrant drug-related behaviors) of successful

care.[40] Whether utilizing developed assessment and monitoring tools or not, it is important to evaluate each case individually to determine the appropriateness of using an abuse resistant or abuse deterrent formulation.

SUMMARY

To counter the growing abuse of prescription narcotics in the United States, many pharmaceutical companies have developed newer formulations of these medications with abuse resistant and abuse deterrent mechanisms. Though significant trials and data of their effectiveness in curbing abuse are lacking, there is promise that these formulations, in addition to the development of newer electronic prescription databases, can be used together to make abuse of these agents more difficult. When prescribing these agents, it is important to analyze and assess the appropriateness of opioid pain management and the utility of abuse-reducing options.

◆   ◆   ◆

REFERENCES

1. Pavuk A, LaMendola B. DEA sees sharp drop in Florida oxycodone sales. Orlando Sentinel. 31 Jan 2012. Retrieved 18 Jul 2012. URL: http://articles.orlandosentinel.com/2012-01-31/health/os-dea-florida-oxycodone-decrease-20120131_1_oxycodone-drug-abusers-pdmp

2. Sutton J. Florida claims success against "pill mills." Reuters. 14 Mar 2012. Retrieved 18 Jul 2012. URL: http://www.reuters.com/article/2012/03/14/us-usa-florida-pills-idUSBRE82D1DS20120314?feedType=RSS&feedName=everything&virtualBrandChannel=11563

3. CDC. Vital Signs: Overdoses of Prescription Opioid Pain Relievers—United States, 1999-2008. MMWR 2011. 60: 1-6

4. Substance Abuse and Mental Health Services Administration (SAMHSA). Results from the 2010 National Survey on Drug Use and Health: volume 1: summary of national findings. Rockville, MD: Substance Abuse and Mental Health Services Administration, Office of Applied Studies. 2011. URL: http://oas.samhsa.gov/NSDUH/2k10NSDUH/2k10Results.htm#2.16

5. SAMHSA. Results from the 2010 National Survey on Drug Use and Health: Summary of National Findings, NSDUH Series H-41, HHS Publication No. (SMA) 11-4658.

6. Stafford K, Gomes AB, Shen J, and Yoburn BC. Mu Opioid receptor downregulation contributes to opioid tolerance in vivo. Pharmacol Biochem Behav 2001; 69: 233–37.

7. Koch T, Höllt V. "Role of receptor internalization in opioid tolerance and dependence". Pharmacol. Ther 2008; 117: 199–206.

8. Corbett AD, Henderson G, McKnight AT, Paterson SJ. 75 years of opioid research: the exciting but vain quest for the Holy Grail. Br. J. Pharmacol 2006; 147: S153–62.

9. Broom DC, Jutkiewicz EM, Rice KC, Traynor JR, Woods JH. Behavioral effects of delta-opioid receptor agonists: potential antidepressants? Jpn J Pharmacol 2002; 90: 1–6.

10. Webster LR, Bath B, Medve RA: Opioid formulations in development designed to curtail abuse: Who is the target? Expert Opin Investig Drugs 2009; 18(3): 255-63.

11. Wang HY, Friedman E, Olmstead MC, Burns LH. Ultra-low-dose naloxone suppresses opioid tolerance, dependence and associated changes in mu opioid receptor-G protein coupling and Gbetagamma signaling. Neuroscience 2005; 135: 247-61.

12. Webster LR, Butera PG, Moran LV, Wu N, Burns LH, Friedmann N. Oxytrex minimizes physical dependence while providing effective analgesia: A randomized controlled trial in low back pain. J Pain 2006; 7: 937-46.

13. FDA. Subutex and Suboxone Approved to Treat Opiate Dependence. Postmarket Drug Safety Information for Patients and Providers. Oct 8, 2002. URL: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm191521.htm.

14. Mendelson J, Jones RT, Fernandez I, Welm S, Melby AK, Baggott MJ. Buprenorphine and naloxone interactions in opiate-dependent volunteers. Clin Pharmacol Ther 1996; 60:105-14.

15. Mueller-Lissner S. Fixed combination of oxycodone with naloxone: a new way to prevent and treat opioid-induced constipation. Adv Ther 2010; 27:581-90.

16. Strain EC, Stoller K, Walsh SL, Bigelow GE. Effects of buprenorphine versus buprenorphine/naloxone tablets in non-dependent opioid abusers. Psychopharmacology (Berl) 2000; 148:374-83.

17. Baum C, Hsu JP, Nelson RC. The impact of the addi-

tion of naloxone on the use and abuse of pentazocine. Public Health Rep 1987; 102: 426–29.

18. Embeda (morphine; naltrexone) package insert. Bristol, TN. King Pharmaceuticals, Inc. 2009 Jun.

19. Badalamenti VC, Buckley JW, Smith ET. Safety of EMBEda (morphine sulfate and naltrexone hydrochloride) extended-release capsules: review of postmarketing adverse events during the first year. J Opioid Manag 2012; 8:115-25.

20. Oxycontin (oxycodone HCL extended-release) package insert. Stamford, CT. Purdue Pharma L.P. 2011 Oct.

21. Ultram ER (tramadol HCl extended-release tablets) package insert. Mississauga, ON. Biovail Corporation. 2008.

22. Exalgo (hydromorphone HCL) extended-release tablets package insert. Hazelwood, MO. Mallinckrodt Brand Pharmaceuticals Inc. 2011 Nov.

23. Leibowitz MT, Zamora CA, Brzeczko AW, Stark JG. A Single-Dose, 3-Way Crossover Pharmacokinetic Comparison Between Immediate-Release Oxycodone Hydrochloride With Aversion Technology (IRO-A, Oxecta), IRO-A With Niacin, and Oxycodone Hydrochloride (Roxicodone) in Healthy Adults Under Fasting Conditions. Am J Ther. 2012. [Epub ahead of print] doi: 10.1097/MJT.0b013e3182456d9b.

24. Oxycodone Immediate-Release, Tamper-Resistant Tablets (Oxecta) National PBM Abbreviated Drug Review. October 2011. VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives.

25. Oxecta (oxycodone) tablet package insert. Bristol, TX. King Pharmaceuticals Inc. 2011 Jun.

26. Setnik B, Roland CL, Cleveland JM, Webster L. The abuse potential of Remoxy(®), an extended-release formulation of oxycodone, compared with immediate- and extended-release oxycodone. Pain Med 2011; 12: 618-31.

27. Richwine, Lisa. US FDA panel rejects King, Acura painkiller. Reuters. 22 Apr 2010. Retrieved 4 Jul 2012. URL: http://www.reuters.com/article/2010/04/22/king-acura-idUSN2223552220100422.

28. Intellipharmaceutics. The Future of Drug Delivery. April 2011. Available at: http://files.shareholder.com/downloads/ABEA-43EQSZ/1329134563x0x454112/1af962f6-fb75-40bb-8cad-70b77474e069/2011_IPCI_Presentation_Mar_24_for_website.pdf.

29. Gershell L, Goater JJ: From the analyst's couch: making gains in pain. Nat Rev Drug Discov 2006, 5:889–890.

30. Butler SF, et al. Development and validation of an opioid attractiveness scale: A novel measure of the attractiveness of opioid products to potential abusers. Harm Reduct J 2006; 3: 5.

31. Butler SF, Black R, Grimes Serrano JM, Folensbee L, Chang A, Katz N. Estimating attractiveness for abuse of a not-yet-marketed "abuse-deterrent" prescription opioid formulation. Pain Med 2010; 11: 81-91.

32. Stauffer J, Setnik B, Sokolowska M, Romach M, Johnson F, Sellers E. Subjective effects and safety of whole and tampered morphine sulfate and naltrexone hydrochloride (ALO-01) extended-release capsules versus morphine solution and placebo in experienced non dependent opioid users: A randomized, double-blind, placebo controlled, crossover study. Clin Drug Investig 2009; 29:777-90.

33. Johnson F, Setnik B. Morphine sulfate and naltrexone hydrochloride extended-release capsules: naltrexone release, pharmacodynamics, and tolerability. Pain Physician 2011; 14:391-406.

34. Coleman JJ, Bensinger PB, Gold MS, Smith DE, Bianchi RP, DuPont RL. Can drug design inhibit abuse? J Psychoactive Drugs 2005; 37: 343-62.

35. Webster LR, Butera PG, Moran LV, Wu N, Burns LH, Friedmann N. Oxytrex minimizes physical dependence while providing effective analgesia: A randomized controlled trial in low back pain. J Pain 2006; 7: 937-46. [Epub ahead of print] doi: 10.1016/j.drugalcdep.2012.05.013.

36. Vosburg SK, Jones JD, Manubay JM, Ashworth JB, Benedek IH, Comer SD. Assessment of a formulation designed to be crush-resistant in prescription opioid abusers. Drug Alcohol Depend. 2012 Jun 20.

37. Tompkins DA, Lanier RK, Harrison JA, Strain EC, Bigelow GE. Human abuse liability assessment of oxycodone combined with ultra-low-dose naltrexone. Psychopharmacology (Berl) 2010; 210: 471-80.

38. Butler SF, et al. Development and validation of the Current Opioid Misuse Measure. Pain 2007; 130: 144-56.

39. Wilsey BL, Fishman SM, Casamalhuapa C, Gupta A. Documenting and improving opioid treatment: The Prescription Opioid Documentation and Surveillance (PODS) System. Pain Med. 2009; 10: 866-77.

40. Passik SD, et al. A new tool to assess and document pain outcomes in chronic pain patients receiving opioid therapy. Clin Ther 2004; 26: 552-61.

CLINICAL TRIAL UPDATE

Use of selective and non-cardioselective beta-blockers in patients with respiratory disease and heart failure — Beta-blockers have been clearly shown to improve mortality in patients with heart failure (HF) caused by left ventricular systolic dysfunction (LVSD). Given the overlap of beta-receptors in cardiac (β1 predominantly) and pulmonary (β2 predominantly) tissues many clinicians are hesitant to prescribe beta-blockers in patients with pulmonary disease, such as chronic obstructive pulmonary disease (COPD). The use of cardioselective beta-blockers has been one strategy proposed to provide cardiovascular benefit while minimizing pulmonary adverse events, although it has not been prospectively determined to be a superior strategy. Therefore, the use of beta-blockers in patients with both COPD and HF remains a challenging clinical scenario.

Using data from the OPTIMIZE-HF regist,ry Mentz and colleagues evaluated the interaction between beta-blocker selectivity in patients with COPD following an admission for HF.[1] The original OPTIMIZE-HF registry enrolled 48,612 patients hospitalized with new-onset or worsening HF. A "follow-up" subgroup was prespecified which included those patients followed for 60 to 90 days after hospital discharge; approximately 12% of the overall study population was included in this subgroup (n=5701).

The present analysis included only those patients in the "follow-up" subgroup with LVSD (n=2682); 725 of these patients (27%) had comorbid COPD in addition to LVSD while 1957 had only LVSD. Of the patients with COPD, 27% received a cardioselective (CS) beta-blocker while 43% received a non-cardioselective (non-CS) beta-blocker; 30% of subjects did not receive a beta-blocker. For those with only LVSD, 31% received a CS beta-blocker, 45% a non-CS beta-blocker, and 24% did not receive a beta-blocker. Overall, carvedilol and metoprolol succinate accounted for 58% and 20% of beta-blockers used, respectively, and were the most commonly used beta-blockers within their respective beta-blocker class (non-CS and CS, respectively).

The associations between CS and non-CS beta-blockers on 60-day mortality and 60- to 90-day mortality or rehospitalization were analyzed through regression modeling; covariate predictors were included in the models to adjust for potential confounders.

At discharge, patients with COPD were less likely to receive beta-blockers than those without COPD (p=0.001). Among those receiving beta-blockers, approximately 40% received a CS beta-blocker while 60% received a non-CS beta-blocker, which was consistent regardless of COPD status.

Estimates of 60-day mortality were similar for those with and without COPD at 6.2% and 6%, respectively. Additionally, mortality rates were similar in those without and without COPD receiving either a non-CS or CS beta-blocker. No beta-blocker use was associated with a higher rate of mortality regardless of COPD status.

The composite outcome of 60- to 90-day mortality or rehospitalization occurred more frequently in those with COPD (41%) compared to those without COPD (34%). Event rates were similar in patients with COPD who received a CS beta-blocker (43.6%) and in those who did not receive a beta-blocker (44.1%); those receiving a non-CS beta-blocker had a lower event rate (37.7%).

Overall, the use of a CS or non-CS beta-blocker was associated with a lower 60-day mortality compared to no beta-blocker use, regardless of COPD status. With respect to specific beta-blocker subtype, there was no significant difference found between non-CS and CS beta-blockers for 60-day mortality (p=0.82). Similar doses of beta-blockers were achieved in both groups, indicating that those with COPD tolerated the agents as well as those without COPD.

The authors concluded that potential changes in pulmonary function with non-CS beta-blockers, as compared to CS beta-blockers, are not associated with worse outcomes in patients with COPD and HF Instead, the potential pulmonary derangements caused by non-CS beta-blockers may be balanced by beneficial cardiovascular effects. Therefore, the preferential use of CS beta-blockers in those with concomitant COPD and HF is not supported by the results of the present study. The authors note that these results should be validated in prospective randomized studies.

1. Mentz RJ, et al. Am J Cardiol 2012 Nov 29. doi:10.1016/j.amcard.2012.10.041