The Long-term Safety and Efficacy of Opioid Analgesics for Chronic Pain

Summary of Expert Meeting held August 12 &13, 2013

Meeting Background

On August 12-13, 2013, the Clinical Trials Transformation Initiative (CTTI) held a meeting to discuss the long-term safety and efficacy of extended-release and long-acting opioid analgesics for chronic non-cancer pain. In a previous public scientific workshop on analgesics, a critical need for evidence of the long-term effectiveness (>12 weeks) of opioids for chronic pain was identified.[1] Following the public workshop a small group of experts in pain management and related specialties, clinical trialists, biostatisticians, and regulators met to draft a protocol synopsis for a trial to evaluate the whether opioid analgesics have long-term efficacy in patients with chronic pain.

The objectives of this CTTI meeting were to engage multiple stakeholders in a discussion of ways to evaluate the efficacy of long-term opioid use, including a discussion of the long-term efficacy protocol synopsis, and to discuss how to evaluate the associated risks. To achieve these objectives, CTTI convened a group of experts from academia, industry, government agencies, and patient advocacy groups.

Review of Evidence

The previous public workshop devoted several presentations to existing scientific evidence on the efficacy and effectiveness of opioid analgesics for chronic pain. For the CTTI meeting, Jane Ballantyne of the University of Washington was asked to present an overview of this evidence. Dr. Ballantyne's presentation showed good evidence of the short-term efficacy of opioids to decrease nociceptive and neuropathic pain, but found a lack of good quality evidence of long-term efficacy in the setting of chronic pain. In addition, Dr. Ballantyne presented information correlating long-term use of opioids in chronic pain with poorer clinical outcomes. She also noted that, in general, safety outcomes from clinical trials are not necessarily generalizable to the overall chronic pain population as they reflect data collected from narrow pain populations that exclude patients at greater risk for adverse events, especially those on higher opioid doses, with mental health comorbidities, and at high risk of addiction.

There was general agreement among meeting participants that more data are needed, and a lot of discussion about the kinds of data that should be collected.

Questions identified around evidence of long-term treatment of chronic pain with opioid analgesics included:

1. Is there efficacy beyond 12 weeks?
2. Does treatment improve function and quality of life?
3. What is the risk of addiction and what are the characteristics of patients who are likely to become addicted? When does the risk for addiction begin?
4. What factors underlie dose escalation over time?
5. What are the characteristics that distinguish which patients stay on opioids long-term, which do not require dose escalation, and which continue to respond and do well?

[1] *Assessment of Analgesic Treatment of Chronic Pain: A Scientific Workshop, May 2012.* http://www.fda.gov/Drugs/NewsEvents/ucm283979.htm

6. How can clinicians identify patients who are likely to benefit (or not to benefit) from long-term treatment with opioids?
7. How can physicians and patients be educated about the potential for addiction and abuse?
8. What are the realistic expectations for outcomes in the medical management of chronic pain? How can prescribers and patients be educated about realistic expectations about the efficacy of opioid analgesics and understanding that medication is only part of a comprehensive pain management regimen?
9. Is there a causal relationship between opioid dose and long-term safety?
10. What are useful clinical protocols for titrating people off opioid medications?
11. What is the best approach for studying long-term use of opioids for chronic pain? For which questions are observational studies appropriate vs. randomized controlled trials? The combination of creating a registry and then embedding randomized clinical trials within the registry was discussed.
12. What important variables must be considered when developing more evidence on long-term opioid use, e.g., indication, ancillary treatment, underlying disease, payor (private insurance vs. Medicaid vs. self-pay), predisposition to addiction, metabolism differences, and variable standard of care. Many or all of these issues are filtered out of RCTs.
13. What ancillary treatments (e.g. gabapentin, SSRIs/SNRIs) have opioid sparing effects? Patients and providers would benefit from more RCT data on which ancillary treatments are beneficial for what indications and then disseminating this information more widely than the pain management field.
14. How can electronic health records (EHR) be used to answer questions about patient outcomes on long-term opioids? The integration of patient reported outcomes into electronic health records and being able to report data back to providers and researchers in a meaningful fashion needs innovative work. Advances in EHR based research could potentially help fill the void/answer questions about the discrepancies between clinical trial data and epidemiological data on the efficacy and effectiveness of long-term opioids for chronic pain.

Review of Proposed Efficacy Study

A protocol synopsis for a randomized clinical trial was developed in late 2012 with the primary objective to evaluate whether opioid analgesics have long-term efficacy in patients with chronic pain. The protocol described a randomized withdrawal design in which patients with a history of chronic pain treated with opioid analgesics for at least one year would be randomized to remain on an opioid, slowly tapered to half the prior opioid dose, or tapered complete off the opioid. Pain scores at the end of the study period would then be compared to baseline pain scores prior to randomization.

The protocol synopsis represents a first step in developing an appropriate study to evaluate long-term opioid efficacy, and was discussed at length by the meeting participants. While most of the attendees agreed that the protocol was a good starting point and were in favor of proceeding with modifications, several issues were raised, including the following:

- Recruitment. There were major concerns about the ability to enroll patients in a trial where they are randomized to continue on opioid, tapered to half their dose of opioid, or tapered to placebo. One reason for potential low enrollment included lack of perceived benefit because patients would not be getting any new therapies and may have their existing therapies reduced or removed. In addition, patients were to be excluded if they reported an interest in participating in the trial as a means of discontinuing their opioid. This exclusion would eliminate patients who may be interested in participating because they struggle with issues of whether to continue an opioid due to adverse effects, social stigma, negative media coverage, expense of copay, and doubts if the opioid is helping. In contrast, potential reasons patients may be likely to enroll include altruism and the desire to know if the medication is truly beneficial.

- Pilot Study. A front-end study to test some of the recruitment/feasibility concerns was discussed. A small, target enrollment of 50, opioid taper study is currently being conducted at the University of Washington and may provide some information about the feasibility of the larger proposed study.

- Pain scale as an outcome. There are many long-term outcomes besides pain that could be measured, such as quality of life, serum levels and functional status. However, gathering additional data may increase the sample size and expense of the trial. Extensive research has shown that the pain scale is an effective measure. The proposed study is powered to detect a treatment difference of 1.25 on the numerical rating scale (NRS) of average pain in past 24 hours. Some argued that this was a larger difference than required in other pain trails (0.45 mentioned). While others noted that a difference of 2.0 was required to be clinically significant.

- Mixed indications. The protocol sought to include patients with painful osteoarthritis (OA), musculoskeletal lower back pain (LBP), and painful diabetic peripheral neuropathy (DPN), or postherpetic neuralgia (PHN). A question was raised about the loss of sensitivity due to mixed indications. As a starting point, the group may want to consider one musculoskeletal group and one neuropathic group. However, others argued that mixed indication should not matter as the trial is randomized and the question proposed in the protocol is fairly simple: is there evidence of long-term effectiveness?

- Inclusion criteria. The protocol includes patients with pain intensity ratings of $\leq$ 7.5 and on a pre-study opioid dosage of $\leq$ 300 mg morphine equivalent. There was some concern that patients with severe pain should be included to allow results to be applicable to this group. However, that would mean including patients who had been on opiates for longer than a year but still have severe pain. Taking such a patient off opioids may not be feasible.

- Sample size considerations. The protocol synopsis authors stated that the baseline study subgroup considered most informative and having the greatest assay

sensitivity are patients with low pain intensity (≤4) who are on a high dose of an opioid. The hypothesis is that this group is likely to develop increased pain when withdrawn to a placebo or a half dose. Some meeting attendees advocated for only enrolling patients with pain scores ≤4.

- Taper. In clinical practice it is a very difficult and lengthy process to withdraw patients completely from opioids. An 8-week taper phase is proposed in the protocol. This may be too fast and withdrawal symptoms may cause differential dropout, especially in those on high doses. While flexible tapering may not be feasible in a randomized, controlled clinical trial, a suggestion was made to modify the protocol to include two taper speeds. It will be important to collect data during the taper phase to assess the patient's progress. A front-end pilot study enrolling only high opioid dose patients was suggested to evaluate the best method and length for tapering opioid and measure number of dropouts.

- Half-dose group. A third of the patients will be titrated to half their prior daily dose of opiate. This would give researchers an opportunity to determine what effect a reduced dose has on pain. There was concern that the withdrawn-to-placebo group may have a large number of drop-outs, and a half-dose arm would allow the researchers a second opportunity to gain information from the trial. This group also offers the opportunity to assess hyperalgesia. There was general agreement in the value of a half-dose arm.

- Active placebo. The proposed placebo was one half a Lomotil tablet (1.25 mg diphenoxylate hydrochloride and 0.0125 mg atropine sulfate). The rationale for Lomotil was that it is constipating like opioid analgesics. However, the use of a constipating agent as a placebo may reduce enrollment and add to the perception that the patient gets little benefit from the trial. In addition, while every attempt will be made to keep patients blinded to their treatment, there are side-effects associated with psychoactive drugs that are unmatchable. Attendee opinions on the most appropriate placebo - a true placebo, a combination of diphenoxylate hydrochloride plus atropine sulfate or just diphenoxylate – were mixed.

- Un-blinding. If a patient is enrolled early in the trial and is tapered or on placebo and doing fairly well, at the end of their treatment, should the patient be un-blinded to avoid the dangers of resuming pre-study dose of the opiate?

Existing Data Sources to Evaluate Opioid Analgesic Safety

Christopher M. Jones of the Centers for Disease Control (CDC) gave a presentation on, monitoring opioid analgesic abuse and overdose in the United States. Abuse of opioid pain relievers is a national public health epidemic. The number and rates of deaths, emergency room visits, and treatment admissions related to use and abuse of prescription drugs is on the rise. In 2009, drug overdose overtook motor vehicle deaths as the leading cause of accidental death in the United States, and opioid analgesics were the most common drugs involved. A proportion of these deaths were due to drug diversion, use of a prescribed drug, or a combination, although current surveillance systems make it

difficult to discriminate these differences. Overdose deaths are the most serious outcome, but the non-fatal outcomes of abuse and misuse cause substantial public health problems and increased healthcare-related costs. The CDC uses a number of surveillance systems to track prescribing practices and opioid use and abuse. The Prescription Behavior Surveillance System, which is a new system combining state level prescription drug monitoring programs (PDMPs), and the National Vital Statistics System (NVSS) were discussed. The NVSS is limited by time lags and inability to understand product-specific changes and how they relate to morbidity and mortality; PDMP data are limited by differences between states. To adequately track opioid use and misuse, the charge is to develop a nationwide system to harness PDMP data and link to systems tracking morbidity and mortality.

Paul Coplan of Purdue Pharma, discussed the complexities of the relationship between opioid analgesic dose and overdose risk. Data from two studies using a UK medical records database and a US insurance claims database were presented. High dose, opioid type, sedatives/hypnotics, and increased age all appeared to be correlated with overdose risk. However, comparisons of overdose risk in patients prescribed high vs. low opioid doses may be confounded by different patient types in the groups, and the discussion raised other significant limitations to these analyses which preclude drawing conclusions based on these data. The high proportion of overdoses without recent prescriptions suggests many overdoses may be from non-prescribed opioids. The presentation concluded that limiting opioid dose may not be the most effective way to prevent opioid overdose.

Richard Dart of the Rocky Mountain Poison and Drug Center discussed the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) System, a post-marketing surveillance system that collects timely product- and geographically-specific data. The system uses a mosaic approach to detect use, misuse and diversion and to contribute to the understanding of trends and aid in the development of effective interventions.

William Becker of the VA Connecticut Healthcare System discussed harnessing national datasets to measure safety of opioid treatment, including the National Survey on Drug Use and Health (NSDUH) and three Veterans Affairs (VA) datasets – the Veterans Aging Cohort Study (VACS), the Quality of Opioid Prescribing Dataset, and the Musculoskeletal Pain Cohort. NSDUH provides high validity population-level incidence and prevalence of non-medical opioid use but is limited by lack of linkage to prescriptions. The VA datasets are able to harness the robust VA EHR but have challenges with generalizability and variable outcome validity. Similar to the CDC presentation, Dr. Becker discussed the importance of recognizing several serious toxicities associated with opioid analgesics in addition to overdose and death.

Lynn DeBar of Kaiser Permanente Center for Health Research discussed using integrated health plan electronic medical record (EMR) data to evaluate outcomes associated with clinical services for the treatment of non-malignant chronic pain. The practice-based data contained in the EMR provide a wealth of information and allow for automated case

identification, greater efficiency and reduced costs for clinical trials. While having EMR data is an improvement over claims data, additional quality assurance is necessary to ensure validity and usability. The Kaiser Permanente Center uses a Virtual Data Warehouse, which is a method for standardizing and pooling electronic health data for multi-site research.

The set of systems are not standardized in the methods used to count people or events other than death. Existing surveillance systems lag by years. Efforts are underway to obtain data from systems in a faster manner, harmonize federal surveillance systems[2], and collate and share state prescription drug monitoring programs.

Discussion: Gathering Additional Evidence on Opioid Analgesic Safety

The attendees discussed other ways to evaluate long-term opioid analgesic safety. Gathering additional safety data requires a combination of implementation science[3], databases to understand the problem, and surveillance systems. More information is needed about how often patients prescribed opioids get into trouble. Broader surveillance systems are needed to evaluate the impact on society and those not prescribed opioids. There are a multitude of fundamental questions that could be asked, including: What is the rate of addiction in patients? What are the risk factors for abuse, addiction, and dose escalation? What are the medication errors and the rates of overdose and death? How can we alert patients to the potential for dependency and abuse? How do we train prescribers to recognize vulnerable populations? What is the effectiveness of various educational and risk management programs? Do practices such as treatment agreements/opioid contracts, prescription drug monitoring programs, and regular urine toxicology screens increase safety and reduce addiction/abuse? What is the impact of up-scheduling an opioid analgesic? How do we measure and ensure appropriate access to pain medications?

Some of the suggestions about ways to gather evidence were as follows:

- The need for clear standardized definitions of abuse-related safety outcomes is needed. The Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION) has conducted a systematic review and proposed standard definitions.[4]

- To determine what happens to chronic pain patients who get started on an opioid analgesic, a large simple trial where the primary endpoints are abuse, addiction

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[2] A review of current federal initiatives and literature focused on ensuring the safe use of prescription drugs with the potential for abuse and future opportunities was released in September 2013. http://www.cdc.gov/HomeandRecreationalSafety/pdf/HHS_Prescription_Drug_Abuse_Report_09.2013.pdf

[3] Implementation science is the study of methods to promote the integration of research findings and evidence into healthcare policy and practice. http://www.fic.nih.gov/researchtopics/pages/implementationscience.aspx

[4] Smith SM et al. Adverse event assessment, analysis, and reporting in recent published analgesic clinical trials: ACTTION systematic review and recommendations. Pain, 2013;154:997-1008.

and/or overdose might be effective. A similar study enrolled 11,000 patients with chronic pain and assessed the risk for abuse of tramadol.[5]

- A pragmatic study designed to enroll a cohort of patients and follow them over time would provide information about the fundamental questions mentioned above.
    - Randomize patients to one of four drugs (extended oxycodone, oxymorphone, morphine, and tapentadol) and prospectively evaluate the incidence of addiction, misuse, diversion etc.
    - Inclusion of immediate-release products because many long-term opioid prescriptions are for short-acting medications.
    - Advantages to using a pragmatic study:
        - Could cluster randomize by site eliminating the need to individually randomize.
        - Would capture patients who are traditionally excluded from an RCT due to history of substance abuse, complicated psychiatric co-morbidities, or concomitant medications (e.g. SSRIs).
        - Would enable the study of risk factors in a prospective way.
    - Modern methods of data capture would help reduce to cost of such a study. Use EHR data to collect what you can with more careful assessments of events and behaviors related to abuse, diversion and addiction.
    - There was some discussion about randomizing by different drugs, by extended-release versus immediate-release, or by class. From an economic standpoint, an argument was made for not randomizing and having a registry instead, although many felt strongly that randomized data are needed, there was concern that such data would not be generalizable to "real world" populations.
    - Funding: The Patient-Centered Outcomes Research Institute (PCORI) is funded by the Medicare trust fund to do comparative effectiveness research. Because pain treatment does not fall in the purview of any specific institute at NIH, a case could be made to request funding from PCORI for a pragmatic study. Industry funding may be more difficult if trials are not product specific.

- The FDA has developed a Risk Evaluation Mitigation Strategy (REMS) for extended-release and long-acting (ER/LA) opioids to provide education and training. There was a discussion about the need to assess how well these strategies work.
    - There are staff at FDA evaluating whether the goals of the REMS are being met.
    - The industry working group recently filed a 1-year report on REMS. Physician awareness of REMS is less than desired. Effective strategies for engaging physicians were discussed – utilizing pharmaceutical marketing

[5] Adams EH et al. A Comparison of the Abuse Liability of Tramadol, NSAIDs, and Hydrocodone in Patients with Chronic Pain. J Pain Symptom Manage 2006;31:465-476.

expertise, linking completion of REMS education to a reduction in malpractice insurance rates, and SAMHSA's prescriber's clinical support system. Currently the ER/LA Opioid REMS is voluntary. A governmental requirement for prescriber education in order to receive a DEA#, although it would require legislative change, would be beneficial. Regulatory boards within states could also require prescriber education.

- The limitation of REMS to ER/LA products was chosen because they are per exposure the riskiest opioids. There were several comments about the need to broaden the REMS to cover all the opioids.

- Opioid treatment registry: Divide patients from pain clinics into cohorts and include a group on chronic opioids who are doing well and a cohort who would like to discontinue use. The registry would collect data on background, patient-reported outcomes, diagnosis, baseline characteristics, functional status, ancillary prescriptions, genotype, blood levels, support, and patient education. The desired patient population could mirror the proposed efficacy protocol in that it would include patients on opioid medication for 1 to 4 years. Alternatively, an inception time of where patients move from short-term use to long-term use (12 weeks) was suggested. Community pharmacists and pharmacist groups could be engaged to gather information at time of dispensing. Although not the focus of this meeting, the importance of measuring endocrine adverse effects, falls and fractures, and driving risks are also very important.

- How can we generate evidence about diversion? What is the contribution of a small number of doctors who are prescribing for the purposes of abuse? In a pragmatic trial, diversion could be a study focus to identify how to reduce it.

- Because the data needs are enormous, the question was raised as to whether it would be possible to overlay data collection on the current EHR or use the EHR to generate a national database. There was general agreement that more funding of EHR-related initiatives is needed to make generation of a database possible.

- Bringing patient advocacy groups and patients on board is important. Patient and general population education is needed. There are approximately 10 advocacy groups focused on pain and also the disease specific groups in which pain is a major issue (e.g. rheumatoid arthritis). Because of the stigma of opioid use, increased data collection is often thought of as an invasion of privacy. If patients better understood why additional data is being collected – to better understand efficacy, improve safety, and reduce diversion – most patients would be more willing to participate in clinical research.

Next steps:
There is an urgent need for high-quality clinical information on the safety and efficacy of the long-term use of opioids. Building a consensus between patient advocacy groups, clinicians, regulators, and industry is a crucial next step in gaining enough momentum to develop, fund, and conduct studies to meet identified evidence gaps.