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Impact of Approved Drug Labeling on Chronic Opioid Therapy: Public Hearing: Request for Comments

Please accept this statement regarding Docket FDA-2012-N-1172, Fed. Reg. 77 (244) 75177-75179 (Dec 19, 2012)

1. SUMMARY

The International Adhesions Society (IAS) provides information, advocacy, support and research for patients and families suffering from adhesions, abnormal fibrous tissue connections caused by surgery or disease such as infection or endometriosis. Abdomino-pelvic adhesions patients may develop a syndrome which makes them practically indistinguishable from those diagnosed with interstitial cystitis, dyspareunia, IBS, or lower back pain. The 15-25 million US patients suffering with these conditions experience chronic, unrelenting pain often treated with opioids.

Opioid use must be understood in the wider context of pain. Chronic pain affects over 100 million Americans, costing \$560-635 billion yearly in medical expenses and productivity. The inestimable human cost of addiction and death caused by opioids is part of the larger tragedy of unrelieved chronic pain. Opioids, alone or combined with other drugs account for about 75% of deaths due to prescription drugs. Opioid sales are about \$9 billion but societal costs of opioid abuse and misuse were estimated (2007) at \$56 billion, almost double the 2012 appropriation for NIH, 158 times its budget for chronic pain research and only 30% less than the Federal budget sequester.

After implementing a strategy to mitigate the risks of abuse and misuse of some opioid formulations, FDA is considering limits on indications for the type and severity of pain, and dose and duration of treatment for all opioids.

None of our patients want to take pain medications. We are concerned that the proposals will precipitate a “cold turkey” for millions of chronic pain patients. An integrated policy must be implemented to wean the nation from opioids by funding and developing alternatives such as the one we have evaluated for pelvic pain¹ - PainShield[®] MD Therapeutic Ultrasound - and found to reduce opioid use in some patients. Accordingly, we wish to:

- Ensure access to adequate pain relief for chronic pain patients.
- State why the proposals lack scientific basis, will reduce access to analgesia and are unlikely to succeed.
- Present our own data, generated specifically in response to FDA’s request regarding this issue, involving 2840 patients representative of, conservatively, 30 million Americans with chronic pain related to pelvic, abdominal & spinal adhesions, endometriosis, interstitial cystitis and related conditions. Our data highlight concerns that the proposals will reduce the ability of a large majority (>80%) of these patients to access pain medication or to be reimbursed for it. In these patients, the use of opioids:
 - exceeds 90 days (85.5%), and often more than 2 years (54.8% of patients).
 - sometimes exceeds 100mg morphine equivalent daily (24.3% of patients).
 - treats pain that is less than severe (46.3%).
 - is necessary, even with non-severe pain because other approaches have failed to provide relief.
 - would be regarded as “off-label” in 92.4% of patients if the labeling proposals are implemented.
- Highlight flaws in the approach of FDA and other agencies to this problem, and to propose revisions to:
 - Challenge paradigms that drugs are the modality and opioids are the analgesics of choice.
 - Formulate a coordinated national strategy to deal with prescription drug abuse and misuse.
 - Define FDA’s role in these national efforts without compromising its primary mission.
- Expedite a national strategy on pain prevention, treatment, management, and research, which includes the development of, and access to, pharmaceutical and non- pharmaceutical alternatives to opioid analgesia.

Wiseman, DM, Petree, T. Reduction of chronic abdominal and pelvic pain, urological and GI symptoms using a wearable device delivering low frequency ultrasound. International Pelvic Pain Society; Chicago, IL. 2012, Abstract 42, Poster 29. (www.kevmed.com/ClinicalData.html). We have established a separate company, KevMed, LLC to market this device.

2. INTRODUCTION

We thank the FDA for the opportunity to contribute to the discussion of this significant public health issue.

The International Adhesions Society (IAS)² provides information, advocacy, support and research for patients and their families suffering from adhesions – abnormal fibrous tissue connections. Adhesions are commonly caused by surgery or disease such as endometriosis or infection. Admissions for abdominal and pelvic adhesions rival those for heart, hip and appendix operations with annual direct costs of over \$5 billion. Adhesions cause infertility, bowel obstruction and chronic abdominal or pelvic pain. Long standing abdomino-pelvic adhesions patients develop a constellation of conditions and symptoms including bladder pain, interstitial cystitis, bowel pain, dyspareunia, IBS, and lower back pain. We have termed this CAPPS³ with patients becoming practically indistinguishable from those whose conditions arose from any one of the individual conditions. The 15-25 million US patients suffering with a form of CAPPS experience chronic, unrelenting pain which is often treated with opioids.⁴

Opioid use must be understood in the wider context of pain. Chronic pain has been estimated by the Institute of Medicine (IOM) to affect over 100 million American adults at an annual cost of \$560-635 billion in direct medical expenses and lost productivity.⁵ The inestimable human cost of addiction and death caused by opioids is part of the larger tragedy of unrelieved chronic pain and its devastation of lives, families, and communities. Pain relief is, according to the IOM, a moral imperative, but relief by opioids comes at a high medical, economic and human cost. There is emerging pharmacological evidence that opioids, although providing analgesia, may sensitize to pain and prolong the chronic pain state.

The use of opioids in the USA has quadrupled over the last decade with a per capita consumption greater than that of France, Germany, Spain, Italy and the UK combined. Opioids, alone or in combination with other drugs account for about 75% (16,651) of deaths due to prescription drugs,⁶ in turn accounting for 58% of all drug-related deaths. Although US opioid sales are estimated to be \$9 billion, societal costs (2007) of opioid abuse and misuse were estimated⁷ at \$56 billion, including costs of law enforcement, criminal justice, healthcare and workplace losses. This figure is almost double the entire 2012 appropriation (\$32b⁸) for NIH, 158 times the 2012 NIH budget for chronic pain research (\$358 million)⁹ and only 30% less than the Federal budget sequester.

After implementing a strategy to mitigate the risks of abuse and misuse of extended-release (ER) or long-acting (LA) opioid formulations, FDA is considering limits on indications for the type and severity of pain, and dose and duration of treatment for all opioids.

3. IAS SURVEY OF OPIOID USE IN CHRONIC PAIN PATIENTS

In specific response to FDA's request for comments on this issue, we set out to document the actual pattern of opioid use in the chronic patients we serve. Using the internet based surveymonkey.com platform, 2909 patients considered participation of which 2840 patients did participate in this survey. Due to the large overlap of symptoms, several patient organizations and web sites kindly agreed to publicize this survey among their members.¹⁰ The main findings (see also Appendix) are as follows:

Overall

None of our patients want to take pain medications, much less opioids, whose effects on constipation are a particular cause for concern and reason for them to abandon opioids in favor of excruciating pain. The vast majority, if not all, of the patients we serve are responsible users of these drugs. Opioids are the last resort for many patients unable to find alternative relief.

² www.adhesions.org, see also www.iscapps.org

³ Complex Abdomino-Pelvic & Pain Syndrome- see Wiseman, D. M. Disorders of Adhesions or Adhesion-Related Disorder: Monolithic Entities or Part of Something Bigger-CAPPS? Semin Reprod Med. 2008; 26:356-68.
<http://adhesions.org/Wiseman2008SeminreprodMed26p356CAPPS.pdf>

⁴ Sanchez, R et al. Impact of Long-Term Opioid Treatment on Quality of Life in Women with Chronic Pelvic Pain Who failed Surgical Therapy. J AAGL. 2000; 7:S55. This study of 35 patients with chronic pelvic pain (CPP) concluded that maintenance narcotic analgesic therapy is an option that should be considered in women with CPP when several surgical treatments fail to improve their quality of life.

⁵ www.iom.edu/Reports/2011/Relieving-Pain-in-America-A-Blueprint-for-Transforming-Prevention-Care-Education-Research.aspx

⁶ www.cdc.gov/media/releases/2013/p0220_drug_overdose_deaths.html

Jones, C. M.; et al. Pharmaceutical overdose deaths, United States, 2010. JAMA. 2013 Feb 20; 309(7):657-9.

⁷ Birnbaum, HG, et al. Societal costs of prescription opioid abuse, dependence, and misuse in the United States. Pain Med. 2011; 12:657-67.

⁸ http://www.nih.gov/about/director/budgetrequest/NIH_BIB_020911.pdf

⁹ http://report.nih.gov/categorical_spending.aspx

¹⁰ We thank a number of organizations and web sites for encouraging the participation of their members/audience in this work, including the Endometriosis Association, Interstitial Cystitis Association, Interstitial Cystitis Network, Endometriosis Research Center, Arachnoiditis Society for Awareness and Prevention, EaseNervePain.com, HysterSisters.com, livinginpain.org, drugwatch.com. Acknowledgement of this participation does not imply agreement with the contents of this statement.

Demographics

2840 (7.2% male, 92.8% female) patients over 18, living in the USA, with chronic, non-cancer pain agreed to participate in the study. Participants came from all 50 states plus Puerto Rico, with an average age of 46.8 ± 0.3 (range 18-83) years. 4.8% of respondents were uninsured, 22.1% were covered by Medicare/Medicaid and the remaining 73.1% had employment or other insurance.

The 10 most common types of pain reported (Appendix, Table 1), regardless of duration or severity were: interstitial cystitis (71%), pain during or after intercourse (57%), back pain (53%), vulvodynia or vaginal pain (40%), irritable bowel syndrome (38%), other bladder pain/ pain related to urination (35%), migraine (33%), arthritis or other joint pain (32%), hip pain (31%), pain due to adhesions (29%). Patients reported an average of 7.9 types of pain.

Almost all (97.1%) patients reported some pain lasting more than 2 years. Shorter durations (1.9%, 1-2 years; 0.6%, 6-12 months; 0.2%, 3-6 months; 0.2%, less than 3 months) were also reported.

Respondents reported using (at any time) an average of 2.68 ± 0.04 different opioids (range 1-15, mode 1). The five most commonly used opioids in this population were hydrocodone (27%), oxycodone (20.1%), tramadol (14.9%), codeine (6.9%), and morphine (6.1%).

Effect of proposed label changes on the studied population

Patients provided information about their level of pain, their duration of treatment and the amount of opioids they were using.

a) Limiting indication to severe pain only

46.3% of the respondents would be excluded from per label treatment because their pain is not “severe”. Only 0.8% of the cohort reported “mild” pain.

b) Limiting duration of treatment (Table 2)

54.8% of the cohort reporting opioid use (N=1766) had done so for more than 2 years. 85.5% of the cohort would be excluded from per label treatment because they have used opioids for more than 3 months.

c) Limiting dose to 100mg ME

Using published data¹¹ to compute morphine equivalent dose, 429 of the 1766 opioid users (24.3%), would be excluded from per label treatment.

d) Combining limits

Combining dose and duration limits would exclude from per label treatment a total of 1526/1766, or 86.4% of the patients.

Combining, dose, duration and pain severity limits would exclude from per label treatment 92.4% of the chronic pain patients in this study.

Definitions of Mild, Moderate, Moderate-Severe, and Severe Pain

Respondents were asked to select the lowest number that means to them pain described as “Moderate”, “Moderate to Severe” or “Severe”.

For the 1754 respondents participating in this question, there is significant overlap (Figure 1) of categories when words are used to segment an 11 point numerical scale. This means that attempting to categorize pain by the use of word descriptors will be imprecise. Some patients will be unfairly denied opioids, while others will undeservedly receive them, defeating the object of the exercise.

Patients’ perceptions of physician’s willingness to prescribe opioids, effect of proposed changes

471/1745 (26.9%) of respondents reported that their doctors were reluctant or unwilling to prescribe opioids. Of the 469 of these respondents who further detailed the reasons for this, 27.1% believed, and another 13.6% reported

¹¹ For the proposal regarding equivalent morphine dose to be implemented, this dose would require definition. We used several sources for this calculation, but principally:

<http://www.globalrph.com/narcotic.htm>

<http://opioidcalculator.practicalpainmanagement.com/>

being specifically told that the doctor was afraid of being sued or getting into trouble with law enforcement, the medical licensing board or the hospital administration, in addition to other possible reasons.

Patients (N=1440) reported that the level of pain at which their physicians would currently prescribe opioids is mild (0.6%), moderate (12.7%), moderate-severe (59.4%), and severe pain (27.4%). With the proposed changes, 72.7% of patients would be excluded from per label treatment.

Restricting the indication to “severe” pain, patients (N=1440) reported that their physicians would be less (25.1%) or not willing (6.7%) to prescribe opioids (44.5% did not know how this would affect their doctor’s prescribing).

Restricting the labeled maximum dose, patients (N=1440) reported that their physicians would be less (14.4%) or not willing (5.5%) to prescribe opioids (53.5% did not know how this would affect their doctor’s prescribing).

Restricting the labeled maximum duration of treatment, patients (N=1440) reported that their physicians would be less willing – even for 3 months (12.0%) or not willing (7.4%) to prescribe opioids, with 14% willing to prescribe only up to three months (50.5% did not know how this would affect their doctor’s prescribing).

Including only proffered opinions, 57.3% (pain level limit), 42.9% (dose limit), and 67.5% (duration limit) of patients felt that their physicians would be less willing or not willing to prescribe opioids.

Patients’ perceptions of the effect of proposed changes on their insurance coverage for opioids

Patients believed that the proposed changes would somewhat likely (19.6%), very likely (26.4%) and almost certainly (26.5%) result in insurance denial of coverage for opioids. Only 8.5% felt that this was not likely at all, with 19.1% expressing no opinion.

Overall patient perceptions of the effect of proposed changes on their access to opioids

This question was asked in two slightly different ways, yielding similar results.

Either because of doctors’ willingness or insurance coverage, patients (N=1409) felt their access to pain medication and control will be greatly (62.1%) or somewhat (25.9%) reduced, with 11.9% believing that their access would not change.

In another question (N=1662), patients agreed somewhat (30.7%) or strongly (51.4%) with the statement “*Too many label restrictions will reduce my ability to get pain relief*”. Patients disagreed with the statement somewhat (3.7%) or strongly (2%), with 12.1% offering no opinion.

Overall patient perceptions about the use of opioids

Patients were asked to rate their agreement with a number of statements about opioids (Table 3). Patients agreed somewhat (45.4%) or strongly (30.5%) with the statement “*We need opioid drugs, but I wish there were alternatives that were safer and with fewer side effects.*”

Representative patient comments

We received 986 “freestyle” comments, falling into the following categories or themes.

- Chronic pain patients are responsible users of opioids, please do not treat us like criminals
- Keep the government out of the practice of medicine
- If you understood better how pain affects my life, you will understand why I need medication
- Opioids help us live our lives
- Punish those who are abusing opioids – find other ways to address abuse, you may not succeed but don’t hurt us in the meantime
- There needs to be better insurance coverage for alternative methods of pain relief
- Restrictions on opioids would increase suicide rate among chronic patients and drive patients to obtain drugs illegally
- There needs to be more funding for pain research
- Educate doctors better on the treatment of pain – opioids can be used safely
- Editorial suggestions for our statement
- PainShield[®] MD Therapeutic Ultrasound

Representative comments from these categories are reproduced in the Appendix.

4. FLAWED STRATEGIC APPROACH TO PROBLEM: CHALLENGING THE OPIOID PARADIGM

FDA has stated that it and other policymakers are “*striving to find a balance between minimizing opioid drug abuse and misuse, while simultaneously enabling appropriate access to pain-relieving drugs.*” This “*balance*” statement and hence the strategy that it represents is flawed because it assumes that:

- opioids are the analgesic drugs of choice
- drugs are the treatment of choice for pain

These assumptions demonstrate just how addicted we are *as a society* to opioids. Even if scientifically-based restrictions could be defined to reduce opioid misuse, abuse will continue. Further, we may be lulled into a false sense of accomplishment that we have solved the dilemma of our need for analgesia, with opioids, by reducing slightly the high societal price we are willing to pay for it. Without considering how opioids should be used in the context of other drugs, devices or techniques, the war on opioid abuse and misuse is doomed to failure.

We therefore propose that the guiding principle of any policy related to opioids should strive to “*to find a balance between minimizing opioid drug abuse and misuse, while simultaneously enabling appropriate access to pain-relieving drugs, devices and other modalities.*”

5. PROPOSED CHANGES CONFLICT WITH AND EXTEND BEYOND FDA’S MISSION

The role of FDA in any overall strategy to combat abuse and misuse and achieving “*balance*” must be challenged. Attempts of the kind proposed to limit abuse, however well-intentioned, conflict with, and extend beyond FDA’s mission of “*protecting the public health by assuring that...drugs...and medical devices...are safe and effective.*”¹²

FDA must certainly audit the safety and efficacy of opioids and to determine whether information exists or can be generated to ensure that well trained prescribers can, safely and effectively, select, treat, counsel and monitor patients requiring them. If this is not possible then opioids should not be available at all. But clearly in a large proportion of cases opioids are used safely and effectively.

FDA has sought to understand the complex nature of pain and how its clinical assessment and treatment may differ by patient population, type, etiology, and duration. However, we need to understand how opioids are actually used, to what effect among different medical specialties, and with more complex stratification than FDA’s questions suggest. With such an understanding can we begin to limit the risks of opioids rather than to propose arbitrary restrictions and attempt to justify them scientifically.

There are legitimate questions about the continued effectiveness of opioids in some patients after long term use that would change the risk-benefit relationship in those cases. FDA can support research and education about identifying these patients and treating them by judicious drug withdrawal. Having determined the limits of safe and effective dosing, any arbitrary limits imposed solely to reduce abuse may increase a drug’s risk-benefit ratio by reducing its effectiveness without substantially changing its profile of side effects.

6. ABUSE AND MISUSE TACKLED BY COORDINATED NATIONAL, STATE AND LOCAL EFFORT

With FDA focusing on legitimate use and the prevention of misuse, the wider issues of abuse and misuse must be tackled by a coordinated effort of government and private agencies at every level, foremost of which are:

- Office of National Drug Control Policy (ONDCP)¹³
- Centers for Disease Control
- National Institute of Drug Abuse
- Drug Enforcement Agency

The web sites of these agencies do not convey the impression that there is a coordinated plan. Indeed, even within FDA, the present discussions of label restrictions for opioids must be unified with those relating to the rescheduling of hydrocodone. One agency must be designated to lead this effort, or a separate body created. Several agencies have advocated tackling opioid abuse and misuse through comprehensive programs that include physician, patient and community education, coordination with law enforcement, naloxone distribution¹⁴ and safe drug disposal programs. Proof that such a program can be successful without compromising legitimate access to opioids comes from Project Lazarus,¹⁵ an organization that has reduced substantially opioid related deaths in North Carolina. Of

¹² www.fda.gov/AboutFDA/Transparency/Basics/ucm194877.htm accessed 2/18/13

¹³ www.whitehouse.gov/ondcp/prescription-drug-abuse
www.whitehouse.gov/sites/default/files/ondcp/issues-content/prescription-drugs/rx_abuse_plan.pdf
www.whitehouse.gov/sites/default/files/ondcp/2012_ndcs.pdf

¹⁴ Implementation of Overdose Education and Naloxone Distribution (OEND) programs may reduce deaths from opioid overdose - Walley AY et al. A. Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis. *BMJ*. 2013; 346:f174.

¹⁵ www.projectlazarus.org

course Risk Evaluation & Mitigation Strategy (REMS)¹⁶ and prescription drug monitoring programs (PDMP) must expand to all opioids.

7. OPIOID ABUSE AND MISUSE MUST BE UNDERSTOOD WITHIN WIDER CONTEXT OF NATIONAL POLICIES ON PAIN

Any program addressing opioid abuse and misuse must be understood within the wider context of a national strategy on pain prevention, treatment, management, and research, the responsibility for which¹⁷ has been delegated to the Interagency Pain Research Coordinating Committee¹⁸ (IPRCC). This strategy must include the following elements:

- Promotion of R&D of safer pharmaceutical and non-pharmaceutical alternatives to opioids.
- An expedited FDA approval program for these alternatives.
- An expedited Medicare reimbursement approval program for these alternatives.
- A review of policies to ensure that modalities such as physical and psycho-therapy are adequately reimbursed to ensure effective pain relief.
- Promotion of education about pain and its relief for student and graduate medical practitioners. The IOM report noted that an average of only 11 hours of training was offered in medical schools on this subject. Curricula must include the proper use of non-opioid analgesics and alternative modalities. Physicians need to fully understand how to use opioids and to counsel patients in their safe use.
- The facilitation of implementation by professional medical organizations of practice guidelines about how alternatives should be used before opioids are prescribed.
- Recommendations as to funding these activities given the enormity of the task.
- Time and volume targets for the wider deployment of opioid alternatives.

8. COMMENTS ON FDA'S PROPOSALS TO RESTRICT OPIOID LABELING

We agree with other commentators on the following points, with additional ideas:

- *Off-label prescribing*
Although labeling restrictions will limit the marketing claims of these drugs, the argument that the restrictions will not limit the practice of medicine and still allow “off-label” prescribing is untenable and disingenuous. In an environment of ever-more aggressive malpractice litigation and cost containment by hospitals and insurance providers, physicians will be reluctant to prescribe “off-label” for fear of legal or professional reprisals, and payors may deny coverage for treatments that are “off-label” and “experimental.” Legitimate patients will have reduced access to opioid analgesia. This fear was expressed by more than 80% of patients in our survey of chronic pain patients, which also showed that the use of opioids would be considered off-label in 92.4% of the patients we surveyed, if all three limitations were implemented.
- *Restriction of indication to “severe”*
We are unaware of simple objective methods to quantify pain. Words like “severe” or “moderate” or numerical or analog scales of 0-10 are relative to each patient and have overlapping meanings (Figure 1). A determined patient will soon learn to provide words or scores that will elicit an opioid prescription. Pain that is “moderate” or even mild” but prolonged can still adversely affect a patient. If opioids succeed in treating this pain where other methods fail, then they should be prescribed. 46.3% of the respondents in our survey of chronic pain patients would be excluded from per label treatment because their pain is not “severe”. Only 0.8% of the cohort reported “mild” pain.
- *Indication for Hydrocodone*
The indication of hydrocodone¹⁹, one of the most prescribed and abused opioids, is for “moderate to moderately severe pain,” not including “severe” pain. Is the intent of the proposals to change the indication for hydrocodone completely? We note separate FDA proposals²⁰ regarding the rescheduling of hydrocodone from Schedule III to Schedule II and would welcome clarification on FDA’s overall strategy with regard to hydrocodone.
- *Restriction of maximum dose to 100mg ME*
We agree that the 100mg ME limit is arbitrary. The risk of overdose death does appear related in a continuous (but not discrete fashion) to the maximum prescribed daily dose²¹ but differs by diagnosis, age, gender and race. Among VHA patients the adjusted hazard ratios (HRs) associated with a maximum daily prescribed dose of 100 mg or more, compared with doses of 1-20 mg, was highest among cancer patients

¹⁶ <http://www.er-la-opioidrems.com/twgUI/remis/home.action>

¹⁷ This stems from Recommendation 2-2 of the Institute of Medicine report on chronic pain

¹⁸ iprcc.nih.gov A number of Federal agencies are represented on this committee including FDA

¹⁹ <http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=eeddb567-4fce-451e-abe1-1f74fb5aebf7>

²⁰

www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM325708.pdf

²¹ Bohnert, A S. et al. Association between opioid prescribing patterns and opioid overdose-related deaths. JAMA. 2011; 305:1315-21.

(HR=11.99), lowest in patients with substance abuse disorders (HR=4.54) and intermediate with patients with chronic (HR = 7.18) or acute pain (6.64), suggesting that a maximum dose should be lower in cancer patients and higher in substance abuse patients, further suggesting a distinction between opioid naïve and opioid tolerant patients. Essentially similar patterns were also observed at lower dose levels. The risk of overdose was also found to vary by age, gender, and race. Even if maximum doses could be determined, it must be related to a pre-determined acceptable hazard ratio relative to an agreed baseline and specific to diagnosis, age, gender and race. What increased risk of death is acceptable?

This proposed arbitrary limit fails to consider that the increase in risk is continuous not discrete. Such an arbitrary limit may lull physicians into a false sense of security about the safety of lower doses.

24.3% of the patients in our survey of chronic pain patients reported using opioids in excess of 100mgME.

- *Restriction of maximum duration of treatment to 90 days*
This restriction fails to take into account patients suffering from chronically painful non-cancer conditions, including arachnoiditis, Adhesions Related Disorder (ARD), chronic pelvic pain, endometriosis, IBS and interstitial cystitis. Some of our patients have endured pain for many years or decades. 85.5% of the patients in our survey have been treated with opioids for more than 3 months.
- *Restrictions will limit access to opioid analgesia*
In the absence of viable analgesic alternatives, any one of the proposed restrictions will limit access of legitimate patients to opioid analgesia and increase the demand for illegally obtained opioids or other drugs. In 1923, the U.S. Treasury Department's Narcotics Division (the first federal drug agency) banned all legal narcotics sales and addicts were forced to buy from illegal street dealers.²²
- *Proposals fail to consider the contribution of concomitant medications on opioid abuse & misuse*
Also involved with overdose deaths involving opioids were benzodiazepines (30.1%), antidepressants (13.4%), antiepileptic and antiparkinsonism drugs (6.8%), and antipsychotics and neuroleptics (4.7%).⁶ Placing arbitrary limits on opioids without consideration of concomitant use will likely have little impact.
- *There is no evidence that any of the proposed restrictions will reduce abuse and misuse.*
Gwen Herman, the representative from Pain Connection said it well: *“If we persist in treating this problem as one of classification or labeling, all we are doing is tinkering with the statistics. We may move a drug up or down the pop chart of choice, but we will have done nothing to address the overriding issue of substance abuse.”*

9. ORGANIZATION BACKGROUND AND DISCLOSURES

The IAS (including adhesions.org, and iscapps.org) does not have not-for-profit status and is funded mainly by its owner Synechion, Inc. (www.synechion.com), a research and consulting company specializing in the science and business of adhesions. Founded in 1996 and presided over by this author, Synechion's work is based on an expertise in the field dating back to 1987 and involvement in a large majority of the anti-adhesion products on the market or in development at one time or another.

The IAS has made a number of achievements including the founding of the world's first clinic for the integrated diagnosis and treatment of adhesions at Celebration Health in Florida and the innovative characterization of the problems of ARD and CAPPS³ and their treatment from the perspective of the patient, including the identification of PainShield[®] MD, a portable wearable therapeutic ultrasound device as a novel and effective analgesic treatment option for patients suffering from pelvic pain and related painful disorders. Accordingly, this author founded KevMed, LLC to market PainShield MD. I, and/or my family members have a number of other financial interests in the subject matter of this meeting. Although Synechion, Inc. consults for a number of companies with commercial interests in this subject, this submission has not been solicited by other commercial entities.

/s/ signed by email submission

Sincerely

David Wiseman Ph.D., M.R.Pharm.S.

Founder, International Adhesions Society (IAS), www.adhesions.org

President, Synechion, Inc., www.synechion.com

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²² A history of opium documented by PBS Frontline: www.pbs.org/wgbh/pages/frontline/shows/heroin/etc/history.html, accessed 2/18/13
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APPENDIX: Data detail for IAS Survey on Opioid Use

Table 1: What type of pain do you have and how severe is it?

32 categories of pain were used in this study and sorted according to the presence of pain of any duration. For each type of pain, patients were asked to describe its severity.

| | Duration of pain | | | Severity of pain | | | | |
|---|---------------------|------|------|------------------|------|-----|---------|--------|
| | as % of respondents | | | | | | | |
| | Any | > 3m | > 2y | | Mild | Mod | Mod-Sev | Severe |
| Interstitial cystitis | 71% | 70% | 61% | | 6% | 20% | 53% | 21% |
| Pain during or after intercourse | 57% | 57% | 50% | | 8% | 25% | 42% | 26% |
| Back pain | 53% | 52% | 45% | | 9% | 27% | 43% | 22% |
| Vulvodynia or vaginal pain | 40% | 40% | 34% | | 9% | 28% | 44% | 19% |
| Irritable bowel syndrome | 38% | 38% | 34% | | 20% | 32% | 37% | 10% |
| Other bladder pain/ pain related to urination | 35% | 34% | 29% | | 8% | 26% | 47% | 19% |
| Migraine | 33% | 33% | 30% | | 7% | 18% | 40% | 36% |
| Arthritis or other joint pain | 32% | 32% | 28% | | 12% | 30% | 41% | 17% |
| Hip pain | 31% | 30% | 24% | | 10% | 29% | 43% | 18% |
| Pain due to adhesions | 29% | 29% | 27% | | 5% | 15% | 45% | 36% |
| Leg pain | 29% | 28% | 23% | | 11% | 28% | 43% | 19% |
| Menstrual pain | 29% | 28% | 27% | | 5% | 18% | 36% | 41% |
| Headache | 28% | 28% | 25% | | 11% | 34% | 39% | 16% |
| Neck pain | 28% | 28% | 24% | | 11% | 29% | 42% | 19% |
| Pelvic pain not otherwise described | 28% | 27% | 24% | | 3% | 18% | 48% | 31% |
| Fibromyalgia | 26% | 26% | 22% | | 7% | 21% | 51% | 21% |
| Pain due to endometriosis | 23% | 23% | 21% | | 3% | 12% | 36% | 48% |
| Pain on defecation | 23% | 22% | 18% | | 16% | 29% | 42% | 13% |
| Shoulder pain | 23% | 22% | 17% | | 12% | 33% | 41% | 14% |
| Abdominal pain not otherwise described | 22% | 22% | 19% | | 5% | 23% | 49% | 23% |
| Rectal pain | 19% | 18% | 14% | | 18% | 31% | 40% | 12% |
| Sacroiliac joint pain | 19% | 18% | 16% | | 8% | 28% | 42% | 23% |
| Sciatica | 18% | 18% | 15% | | 10% | 24% | 42% | 24% |
| TMJ pain | 18% | 17% | 16% | | 33% | 32% | 25% | 10% |
| Arm pain | 12% | 12% | 9% | | 14% | 34% | 40% | 12% |
| Other | 10% | 10% | 9% | | 3% | 13% | 46% | 38% |
| Pudendal neuralgia | 8% | 8% | 6% | | 6% | 15% | 43% | 36% |
| Arachnoiditis | 3% | 3% | 3% | | 3% | 7% | 36% | 54% |
| Trigeminal neuralgia | 3% | 3% | 2% | | 17% | 21% | 39% | 23% |
| RSD or CRPS | 3% | 3% | 2% | | 7% | 9% | 43% | 41% |
| Chronic prostatitis | 2% | 2% | 2% | | 13% | 19% | 49% | 19% |
| Phantom limb pain | 1% | 1% | 1% | | 13% | 33% | 42% | 13% |

Of the 2456 respondents, 53.8% would be included since pain is severe (regardless of duration) 0.8%, 6.5% and 39% would be excluded from per label treatment because pain is “only” mild, moderate or moderate-severe respectively.

Almost all (97.1%) patients reported some pain lasting more than 2 years. Shorter durations (1.9%, 1-2 years; 0.6%, 6-12 months; 0.2%, 3-6 months; 0.2%, less than 3 months) were also reported.

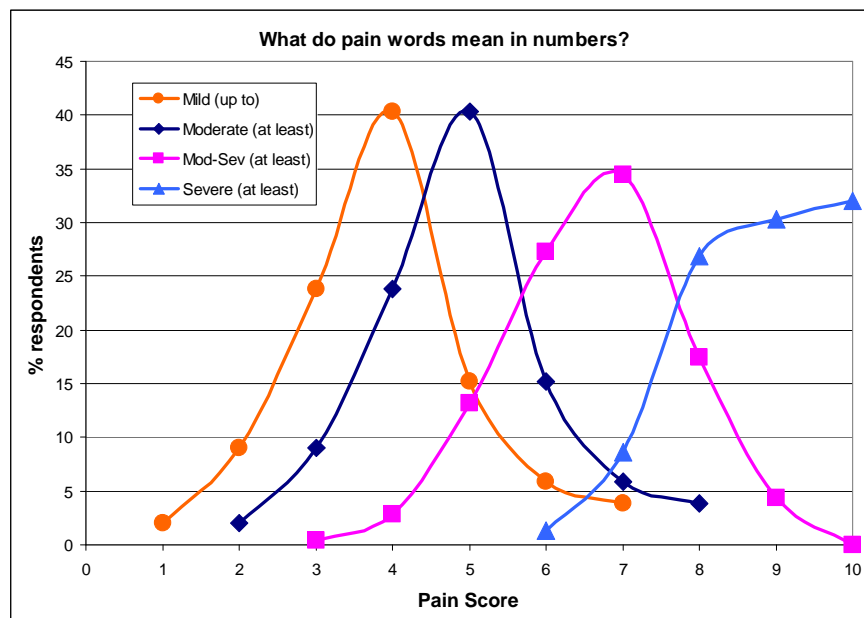
Table 2: Duration of Opioid Treatment

| | N | Subtotal | % | Subtotal |
|-------------|------|----------|--------|----------|
| < 1 month | 151 | <3m | 8.6% | <3m |
| 1-3 months | 105 | 256 | 5.9% | 14.5% |
| 3-6 months | 99 | | 5.6% | |
| 6-9 months | 81 | | 4.6% | |
| 9-12 months | 90 | | 5.1% | |
| 1 -2 years | 272 | >3m | 15.4% | >3m |
| > 2 years | 968 | 1510 | 54.8% | 85.5% |
| Total | 1766 | | 100.0% | |

Table 3: Overall patient perceptions about the use of opioids

| | Disagree | | No opinion | Agree | | N |
|---|----------|----------|------------|----------|----------|-------|
| | Strongly | Somewhat | | Somewhat | Strongly | |
| We need opioid drugs, but I wish there were alternatives that were safer and with fewer side effects | 2.8% | 6.8% | 14.5% | 45.4% | 30.5% | 1,667 |
| Too many label restrictions will reduce my ability to get pain relief | 2.0% | 3.7% | 12.1% | 30.7% | 51.4% | 1,662 |
| I am concerned that opioid drugs can easily be misused | 6.9% | 19.0% | 22.1% | 37.1% | 15.0% | 1,645 |
| I am concerned that opioid drugs may cause addiction | 8.0% | 22.5% | 21.6% | 33.3% | 14.7% | 1,651 |
| I am concerned that opioid drugs burden the country with costs of law enforcement, addiction programs, healthcare for babies born to addicts etc. | 17.9% | 25.2% | 26.8% | 20.9% | 9.3% | 1,640 |
| If safer alternatives were available, imposing more restrictions on opioid prescribing makes sense | 15.6% | 20.5% | 21.7% | 29.1% | 13.1% | 1,654 |

Figure 1: What do descriptions of pain intensity mean to you?



For each respondent the highest number conveying “Mild” pain was calculated by subtracting 1 from the “Moderate” score.

Representative patient comments

We received 986 “freestyle” comments, falling into several categories as illustrated below (comments reproduced without editing for spelling or grammar).

Chronic pain patients are responsible users of opioids, please do not treat us like criminals

- Please highlight the fact that the majority of chronic pain patients take the medication in a responsible way. I use the appropriate dose of medication during IC flare-ups as a last resort when other methods have not relieved the pain and that's it. I don't use them to change my mood, sleep, etc. I am sure that myself and people like me are in the majority. Can you get those figures? (How many people use pain medications in appropriately vs those that abuse it)

- Why must we be punished for the deeds of those addicts who will take any drug they can get on, and then misuse them, so you guys think the people who actually need the drugs can no longer have access to them. It is insane.

- - Chronic pain patients deserve adequate pain management. Chronic pain patients should never be held responsible for the actions of criminals. They most certainly should not be punished for them.

- I am a chronic pain person, I know what and how I should take my medicine, I lock it up at my home and I am safe with my drugs, I do not sell or do anything wrong

- This group of patients are not drug seekers and are monitored for opioid addiction and have random drug screening tests.

- I don't understand how pain medication can be limited or taken away. For those of us who use it responsibly, those who abuse the opioid, make it more difficult for the patient and family, the patient who is truly in pain. Pain is not visible. I feel limiting the amount and duration of an opioid, will cause people to have to deal with the pain constantly.

- Again, most people in chronic pain take their medications as prescribed. We are patients in horrible pain not criminals. I don't want to be on pain medicine but until a cure for IC is discovered I have to be on pain meds.

Keep the government out of the practice of medicine (very common comment)

- I feel that the physician should be allowed to prescribe medications as needed by his or her patients, based on their knowledge of the particular patient, and the federal government should not be involved in those decisions.

If you understood better how pain affects my life, you will understand why I need medication

- Whoever these FDA people are, let me wrap a barb wire around there genitals and lower back and see how well they enjoy their days and nights trying to do simple things like walk, sit, stand, sexual intercourse.

- Please stress in stronger terms that the lower quality of life of someone suffering from unremitting chronic pain with no access to relief will essentially take that person out of society, make them unable to hold a job or care for their children and will cause them to be a burden on society. I am sure that paying lifetime disability payments is more expensive than putting someone through rehab. I have never missed a single day of work due to IC because I am able to treat my symptoms appropriately.

- The people behind changing or reducing the pain meds have obviously never been in true and unrelenting pain that does not stop UNLESS we DO take narcotics, which are the only type of relief we have. What gives the government the right to tell us how bad our pain is?

- I'm crying as I'm writing this. Tired, in pain, can't eat (very restricted diet) and confused. I can't imagine if this were to go into . What would I do? How much of a burden to my family I already am, and I'm ashamed of that. Hydro is the only med that keeps me from falling off a cliff.

- So-called "mild" pain that lasts a lifetime will render a patient as immobile as another who is suffering through "severe" pain on their first day of a broken leg. When pain is chronic, the common understanding of "pain" ceases to be applicable. When most people experience physical pain, they are able to deal with it because of the subconscious assumption the pain will end

- Over reaction by the FDA will severely impact those suffering from physically unbearable, psychologically debilitating chronic pain. There should be a committee of people who actually suffer from these conditions who make these kinds of decisions. If one has not experienced the hell of chronic pain themselves they will not understand or exercise proper empathy or judgement with these restrictions. The addicts in society will find a way no matter what the FDA does. Chronic pain sufferers should not have to pay the price for abusers!!!!!! This is inhumane!!!!

- When you have been diagnosed with IC please tell me how it feels and if you would want pain medication at times

Opioids help us live our lives

- Opioid drugs are the difference between being able to have a life worth living or not wanting to continue a life of constant suffering to the extreme. Until YOU HAVE THIS PAIN, you can not know. You have no right to take away my only life I choose to continue. And, that would be with the ONLY TRUE PAIN Relief and that is OPPIATES !

- People only seem to want to see the bad side of Opioids. They need to see the good things it does. We don't want to take pain pills. I would love to be able to get up in the morning & have a life w/o them

- In order to work, I need the medication.

- Yes, there need to be alternatives, but let's not take off the table what works!

- Opioid users know the risk. The side effects outweigh the risks. Dealing with Chronic Pain takes pieces of your life away. Taking Pain Meds. helps to get a little bit of your life back.

- - I have been through many treatments. Pain management of my hydrocodone works. It allows me to have a life that is bearable with pain medication; otherwise, life is not worth living. I went two weeks without hydrocodone and was in such intense pain i did not want to live. I could not walk. I could not stand up straight. I held my pelvic/bladder area all the time. I cried. I could not sleep

Punish those who are abusing opioids – find other ways to address abuse, you may not succeed but don't hurt us in the meantime

- Advocate for stiffer penalties for patients who are caught selling their prescription opioids.

- - Arrest the idiots that are misusing. Leave us that have chronic, documented illnesses alone. Leave the decision up to the doctor. I have IBS, when I am constipated that means I have normal bowel movement so I actually am relieved, Don't waste the time on formulating another committee of idiots. REhabilitate the ones getting free rides and that are playing the system and getting/abusing the drugs-FIX THAT FIRST before you mess with people like me.

- There are better ways to address the drug abuse problem in our country than to consign people like me to a living hell of untreated pain.

- Even though I deal w chronic pain, I can't agree with the continued, easy access that our country has to prescribed drugs. Spend a day working in a "pain clinic" or working along side law enforcement and you will see how rampant this problem is in our country.

- Drug abusers are going to abuse drugs no matter what the FDA decides. Addiction is a separate matter that only the individual can address. It is therefore cruel to the rest of us ---with no end to pain or cures available---to not receive the pain relief we desperately need, The War on Drugs was lost a long time ago, and trying to regulate addicts is a useless waste of money. They will not be regulated, just work harder to get their drugs through crime and illegality.

There needs to be better insurance coverage for alternative methods of pain relief

- I had some relief w an internal vaginal tens unit but ins. Co - blue cross- would not cover!!! Ridiculous. Also, I forgot that I tried vaginal Valium which relaxed the muscles- ins did not cover THAT either!!! So frustrating how they dictate our care!

- - My doctor tried to get approval for a Spinal Cord Stimulator so I might get pain relief and not have to take opioid's but my insurance denied it!!!! The cost is more than I can pay for out of pocket. Until you can get such devices approved for my pain that the insurance companies will pay for, I have to take pain meds to have any quality of life!

- - Should include: until insurance companies embrace Eastern medicine and see the effectiveness of non drug therapy, and are willing to cover the cost of such therapy then the need for opioids is necessary.
- The FDA should instead look to mandatory coverage for alternative medicine, specifically chiropractic and massage therapy. That would help alleviate some pain and allow patients to take less medication.
- I would add a section that speaks to the need for affordability regarding alternative solutions, especially for those on Medicare/Medicaid or with no insurance. I would also like to see something about the continued availability of opioids for those who cannot or choose not to use the alternative solutions.
- The lack of resources forces suffering patients to look outside the US for treatment. This is a deplorable state of affairs for patients living in the US!

Restrictions on opioids would increase suicide rate among chronic patients and drive patients to obtain drugs illegally

- The point must be made that those of us with unrelieved severe pain may opt for suicide or blackmarket methods - even more dangerous-than to spend a life confined to bed with no real quality of life. Forseeing this intrusion of the federal medical bureaucracy, many of us are looking at the use of medical marijuana.as a possible fallback. We will be forced to find pain relief in some form. The figures on deaths would need to be modified as many of these deaths are due to recreational drug use. No one I know who has adhesions or IC or IBS is trying to get "high"...we just want to be able to live the best life we can without the crippling effects of pain.
- How many deaths would be caused each year due to suicide as related to pain? I have considered it many times when I am in such severe pain and cannot get adequate relief even from my opioids. This is something that needs to be considered. I know I am not alone in this feeling
- - Never mind 32B in societal costs, just think of what would happen if chronic pain patients were bed bound cause they couldn't have access to pain medication. Imagine the mass suicides and hopelessness that would incur if we can't have access to pain medication. THAT WOULD BE THE LARGEST TRAGEDY. That's no quality of life. The FDA needs to go after criminals not patients.

- They simply think we are drug seekers. If we cant get any medicine what are we to do? Not work, get it off the street?

There needs to be more funding for pain research

- If opioids are going to be eliminated then there needs to be funding provided for treatment research.
- More money on research is needed

Educate doctors better on the treatment of pain – opioids can be used safely

- We need Drs to be educated on pain control rather than judging the person who is seeking it. They have to arm themselves with other tools. Pain isn't something you can SEE- Drs have to listen, pay attention and seek counsel when they feel it's needed. I feel I have a responsibility to myself and my Dr to control these drugs, I have a job, I am a mother and grandmother and a wife to a VERY supportive responsible husband (a Dr himself). Unfortunately, opioids are the most affordable drug to obtain.
- opioids are safe and helpful when used correctly
- Provide easy access to opioids as needed for pain treatment, under medical supervision. Continue education to prevent drug abuse and misuse.
- also think we need to educate some doctors on chronic pain.

Editorial suggestions for our statement

- I would rewrite the lead in as follows: "Patients who take pain medication do so in order to function. They would not choose to take pain medications otherwise but understand and appreciate that often the access to pain medications is the difference between a productive day and a day spent in bed unable to accomplish anything besides the pain. These patients would welcome non-opioid alternatives to pain, but unless and until such alternatives are proven effective and are widely available, our objectives in formulating this response are to:

PainShield® MD Therapeutic Ultrasound

We received a small number of comments questioning, understandably, our mentioning of PainShield MD. We also received comments welcoming its inclusion in the discussion.

Our work with patients with chronic pelvic and abdominal pain predates by many years our work with PainShield MD. Our track record of advocating for patients in an unbiased manner speaks for itself. However, since we have now (albeit in the context of the IAS) investigated and launched a company (KevMed) to commercialize this device we are duty bound to disclose this potential conflict of interest.

Beyond this, we feel that mention of this device exemplifies the efforts that should be put into dealing with pain. For too long, patients have bemoaned the lack of progress in alleviating these conditions. In an economy that has been unkind to such progress, we conducted and funded this work on our own, with no outside help other than the grassroots support of patients through our web site. We also hope that if ever we are to profit from PainShield MD, we will continue to fund the IAS as well as groups such as the ones who enthusiastically supported this work.

It is understandable why our efforts might be viewed with a jaundiced eye in the context of a traditional model of a biomedical company which supports patient advocacy (often only at a perfunctory level) as a means to sell its product. Our track record and *raison d'être* is that our commercial efforts are a means to further the cause of patients.

It would have been in our best interest to see the proposals implemented forcing patients to seek alternatives such as PainShield MD. Instead, we have put significant effort into conducting this work and advocating for the patient in the most balanced manner possible. We make no apologies for celebrating the achievement that PainShield MD represents to a grassroots patient group such as the IAS, for advocating that it should be used as a model for others to emulate, and to illustrate one way of tackling the problem of pain through alternatives. We welcome the development of other alternatives as well as the commitment of the companies developing them to advance the cause of chronic pain patients as we are striving to do.

This document can be found at: www.synechion.com/IAS2013-FDA-OpioidSurvey.pdf