Fact Sheet on FDA Epidural Steroid Warning, Safe Use Initiative, and the MPW Approval of 17 Regulations to be Instituted by the FDA

ISSUE:
It has been reported that the FDA will be issuing a statement that epidural injections are not only catastrophic, but also ineffective, and must not be used, without determining their efficacy by assessing the available evidence.

The FDA also has a public hearing scheduled for November 24 and 25.

BACKGROUND:
On April 23, 2014, the FDA issued a drug safety communication which required label changes to warn of rare but serious neurologic problems after epidural corticosteroid injections for pain. The warning specifically stated the following:

- The FDA is warning that injection of corticosteroids into the epidural space of the spine may result in rare but serious adverse events, including loss of vision, stroke, paralysis, and death.

- Injecting corticosteroids into the epidural space of the spine has been a widespread practice for many decades; however, the effectiveness and safety of the drugs for this use have not been established, and the FDA has not approved corticosteroids for such use.¹

The controversy beleaguering this issue revolves around the inaccuracies of this warning, the inadequate literature review and the subsequent faulty conclusions drawn from these reviews, all of which have been extensively discussed.²³⁴

Despite an official appeal by the American Society of Interventional Pain Physicians (ASIPP) and an appeal letter with the signatures of 1,040 practicing interventional pain physicians,⁵ the FDA has continued its

misguided efforts, culminating in a favorable decision and approval by a self-appointed “consensus” organization called the Multi-Society Pain Workgroup (MPW). The major participant of this workgroup, the American Society of Anesthesiologists (ASA), along with the International Spine Intervention Society (ISIS), proposed a set of approximately 20 regulations and potential publication of manuscripts. They were basically rejected and not based on evidence and were even more inaccurate than the FDA warning itself. Subsequently, the FDA, setting its Safe Use Initiative Committee aside, obtained nominal approval by the MPW without an evidence assessment or even consensus of the society members that was announced on August 1, 2014. The International Spine Intervention Society (ISIS) stated that they felt the alert was misleading in its message regarding the safety of epidural steroid injections and contained inaccuracies regarding the effectiveness of this procedure. However, they have approved almost all of the 20 safety recommendations, changing them to 17 which are identical to those considered by the Safe Use Initiative.

THE INAPPROPRIATE PROCESS OF DEVELOPMENT OF REGULATIONS:
The MPW issued press releases which they considered as achievements on their respective Web sites. In its press release, the MPW claimed that it was originally formed to assist Medicare contractors in developing more consistent local coverage determinations (LCDs) through multisociety consensus recommendations. Furthermore, the MPW also claimed that based on its track record in generating consensus and producing multisociety recommendations on interventional pain management issues, the MPW was selected by the Safe Use Initiative leaders as the logical body to develop recommendations on the safe use of epidural steroid injections. They failed to disclose the unfavorable results of these determinations that were developed without proper evidence assessment. No reasons have been given why they have adopted the same ASA and ISIS recommendations which were rejected by an expert panel of the Safe Use Initiative. They further claimed that the MPW process, which results in majority consensus recommendations, is entirely democratic, transparent, and collaborative with no single society having more influence than any other participating society—a fact that has been vigorously argued. The societies represented on the MPW are:

1. American Academy of Neurological Surgeons (AANS)
2. American Academy of Pain Medicine (AAPM)
3. American Academy of Physical Medicine and Rehabilitation (AAPM&R)
4. American College of Radiology (ACR)
5. American Pain Society (APS)
6. American Society of Anesthesiologists (ASA)
7. American Society of Neuroradiology (ASNR)
8. American Society of Regional Anesthesia (ASRA)
9. American Society of Spine Radiology (ASSR)
10. Congress of Neurological Surgeons (CNS)
11. International Spine Intervention Society (ISIS)
14. Society of Interventional Radiology (SIR)

As shown in its own statement, upon its inception ASIPP was involved in the MPW. In fact, although this is partially accurate, ASIPP subsequently resigned from participation. The MPW includes 4 surgical societies [American Academy of Neurological Surgeons/Congress of Neurological Surgeons (AANS/CNS), North American Spine Society (NASS), North American Neuromodulation Society (NANS)]; 4 radiology societies: [American College of Radiology (ACR), American Society for Neuroradiology (ASNR), American Society of Spine Radiology (ASSR), Society of Interventional Radiology (SIR)]; 2 anesthesiology societies: [American

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Society of Anesthesiologists (ASA) and American Society of Regional Anesthesia and Pain Medicine (ASRA); 2 pain management societies, [American Pain Society (APS) and American Academy of Pain Medicine (AAPM)]; one physiatry society: American Academy of Physical Medicine and Rehabilitation (AAPMR); one international society: International Spine Intervention Society (ISIS). The fifteenth society was ASIPP, which has since withdrawn due to dissatisfaction with the process and its inability to convince any of the members to look at the balance of evidence other than what was presented by ISIS and approved by Noridian’s executive carrier medical director.

Of interest, 4 surgical societies and 4 radiology societies together perform less than 10% of the procedures that are performed, constituting a majority (8 of 14) which always followed the direction of ISIS and ASA.
REGULATIONS WITH NO EVIDENCE:
Table 1 shows 20 proposed technical standards for the safe use initiative which were not approved by the members of the Safe Use Initiative.

Table 1. Proposed technical standards in performance of interventional techniques.

<table>
<thead>
<tr>
<th>Proposed technical standards in performance of interventional techniques</th>
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<tbody>
<tr>
<td>1. All cervical interlaminar (IL) injections should be performed using image-guidance, with appropriate lateral or contralateral oblique views, and a test-dose of contrast medium.</td>
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<tr>
<td>2. Particulate steroids may be used with cervical IL ESIs that are performed using image-guidance, with appropriate lateral or contralateral oblique views, and a test-dose of contrast medium.</td>
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<tr>
<td>3. Particulate steroids may be used with lumbar IL ESIs that are performed using image-guidance, with appropriate lateral or contralateral oblique views, and a test-dose of contrast medium.</td>
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<tr>
<td>4. Cervical transforaminal (TF) ESIs should be performed by injecting contrast medium under real-time fluoroscopy and/or DSA, in a frontal plane, before injecting any substance that may be hazardous to the patient.</td>
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<tr>
<td>5. Lumbar TF ESIs should be performed by injecting contrast medium under real-time fluoroscopy and/or DSA, in a frontal plane, before injecting any substance that may be hazardous to the patient.</td>
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<td>6. TF ESI is associated with a risk of catastrophic neurovascular complications.</td>
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<td>7. Particulate steroids appear to be inordinately represented in case reports of neurovascular complications following TF ESI.</td>
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<td>8. Cervical interlaminar injections should preferably be performed at C7-T1, but not higher than the C6-C7 level.</td>
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<td>9. No cervical interlaminar injection should be undertaken, at any segmental level, without reviewing, before the procedure, prior imaging studies that show there is adequate epidural space for needle placement at the target level</td>
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<td>10. Cervical interlaminar ESIs are recommended over cervical TF ESIs</td>
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<td>11. Lumbar TF ESIs are recommended over lumbar interlaminar ESIs when a unilateral single nerve root is involved</td>
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<td>12. Lumbar IL ESI is recommended over TF ESI when there is involvement of several nerve roots unilaterally or bilaterally</td>
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<tr>
<td>13. Dexamethasone, a non-particulate steroid, should be used for the initial injection in lumbar transforaminal epidural injections.</td>
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<tr>
<td>14. Particulate steroids should not be used in lumbar TF ESIs.</td>
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<td>15. DSA is recommended for cervical TF ESIs.</td>
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<tr>
<td>16. DSA is recommended for lumbar TF ESIs.</td>
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<td>17. Extension tubing is required for all TF ESIs.</td>
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<td>18. A local anesthetic injection is recommended before injection of the steroid with all TF ESIs.</td>
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<td>19. Chlorhexidine is preferable as the skin prep solution over iodine-based solutions.</td>
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<td>20. A face mask and sterile gloves must be worn during the procedure.</td>
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Table 2 shows the 17 safety recommendations approved by the MPW that may be either fully or partially adopted by the FDA. Consequently, ASIPP has filed an official appeal\(^7\) with the FDA, based on the essential requirement that appeals may be filed only by nonparticipating organizations. Although ASIPP was not a participant in the MPW, it did participate on the expert panel of the Safe Use Initiative. These recommendations apply to cervical and lumbar interlaminar epidural injections and cervical and lumbar transforaminal epidural injections. It seems that these do not include thoracic interlaminar epidural injections, caudal epidural injections, or thoracic transforaminal epidural injections. Thus, these published recommendations may be divided into 6 categories:

1) Recommendations 4 and 7 specifically related to cervical transforaminal epidural injections;
2) Recommendations 9, 10, and 11 specifically related to lumbar transforaminal epidural injections;
3) Recommendations 2 and 16 applicable to both cervical and lumbar transforaminal injections other than the specific recommendations include;
4) Recommendations 1, 3, 5, 6, and 15 related to cervical interlaminar epidural injections;
5) Recommendations 8 and 15 related to lumbar interlaminar epidural injections and;
6) Recommendations 12, 13, 14, and 17 related to all epidural injections.

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\(^{7}\) Letter to Division of Dockets Management, Food and Drug Administration, Department of Health and Human Services, from American Society of Interventional Pain Physicians RE FDA Citizens Petition, September 3, 2014.
Complications related to epidural steroid injections are accurate in reference to cervical transforaminal epidural injections. Further, these drugs are not approved to be injected into the epidural space by the FDA. However, they have been used similar to numerous other drugs which are used as off-label, specifically in managing chronic pain. It is important that we inform patients that these are off-label uses and also discuss risk-benefit ratios.

Based on the evidence, cervical transforaminal epidural injections have not been shown to be accurate in arriving at a diagnosis and their efficacy has not been demonstrated for chronic pain management.

However, the FDA, MPW, ASA and ISIS have projected all these complications onto all other epidural injections. Cervical transforaminal epidural injections constitute a small proportion of injections. For example, in 2011, cervical and thoracic transforaminal epidural injections constituted 2.9% of all epidural injections, lumbar transforaminal epidural injections constituted 48.5% of all epidural injections, 8.7% were cervical/thoracic interlaminar epidural injections, and 39.9% were lumbar interlaminar epidural injections. These data are based on Medicare data, which usually are representative of the general population. Further, Medicare patients are the most complex patients, with age-related degenerative changes and significant comorbid conditions including pulmonary, cardiac, and neurological disorders.
Thus, none of the 17 recommendations are based on any evidence for 48.6% of epidural injections. These also include and mandate some impossible parameters which will be dangerous to the patient, i.e., injecting in a frontal plane, which requires turning a prone patient supine; using extension tubing, which could increase mechanical risk due to the rotational effect of the extension tubing on the needle, where the needle tip may essentially enter and exit the arterial lumen; use of a face mask and sterile gloves, which is a standard practice and a regulation from the CDC; as well as multiple fluoroscopic views increasing radiation risk, and the risk of the needle being in the epidural space for a longer period of time, or even moved. Consequently, this is extensive micromanaging of the technical aspects of medicine.

**COST OF CHRONIC PAIN AND COMPLICATIONS OF THERAPY:**
- FDA Commissioner Margaret Hamburg, has stated that, “chronic pain is pervasive in 100 million persons in the United States” to justify the approval of Zohydro, against recommendations of the Scientific Advisory Committee.
- A statement in reference to the prevalence of severe chronic persistent pain is inaccurate. This type of pain appears to be in approximately less than 30 million people in the United States (Tables 3 and 4). Even then, with all the risks associated with opioids, the FDA seems to be promoting opioids, whereas the DEA and many states are reducing access to them. Contradictory actions, including changing hydrocodone to Schedule II, have been taken by the FDA. At the same time, all the other techniques with a lot fewer complications than opioids and others are being eliminated without appropriate evidence.
- There have been almost 17,000 deaths each year secondary to opioid overuse and abuse. Further, over 14,000 babies are born each year with opioids and other drugs in their systems (Fig. 1).

**Table 3. Myth of the cost of chronic pain.**
- The annual cost of chronic pain is $560 to $635 billion a year
  - Direct cost due to pain is $261 – $300 billion
- Prevalence estimates
  - 10% moderate pain
  - 11% severe pain
  - 33% joint pain
  - 25% arthritis
  - 12% functional disability
  - Moderate pain $4,516
  - Severe pain $3,210
  - Joint pain $4,048
  - Arthritis $5,838
  - Functional disability $9,680


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Table 4. Total incremental costs of medical expenditures for selected pain conditions (in millions of adjusted 2010 US dollars and millions of persons).

<table>
<thead>
<tr>
<th>Condition</th>
<th>Population (in Millions)</th>
<th>Model 2 (including Functional Disability)</th>
<th>Model 3 (including Functional Disability, Diabetes, and Asthma)</th>
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</thead>
<tbody>
<tr>
<td>Moderate pain</td>
<td>21.3</td>
<td>$39,024</td>
<td>$39,646</td>
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<tr>
<td>Severe pain</td>
<td>22.6</td>
<td>$58,144</td>
<td>$60,000</td>
</tr>
<tr>
<td>Joint pain</td>
<td>70.3</td>
<td>$48,280</td>
<td>$45,630</td>
</tr>
<tr>
<td>Arthritis</td>
<td>53.4</td>
<td>$61,071</td>
<td>$59,292</td>
</tr>
<tr>
<td>Functional disability</td>
<td>24.7</td>
<td>$93,529</td>
<td>$88,680</td>
</tr>
<tr>
<td>Total</td>
<td>100.0</td>
<td>$300,048</td>
<td>$292,257</td>
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NOTE: Dollar amounts were adjusted for inflation as of 2010 using the Consumer Price Index Medical Care Inflation Index. This analysis is based on the total noninstitutionalized adult subpopulation of the United States for individuals aged 18 or older, who represented 210,764,398 individuals as of 2008. Model 2 includes functional disability in addition to all the other control variables. Model 3 includes functional disability, asthma, and diabetes in addition to all the other control variables. One hundred million persons had at least one of the pain conditions studied. The population total for the selected pain conditions does not sum to 100 million because some persons have multiple conditions.


Fig. 1. Opioid-analgesic poisoning related deaths.

Source: http://www.cdc.gov/nchs/data/databriefs/db166_table.pdf#4
A simple over-the-counter product such as Tylenol has been linked to as many as 980 deaths in a year to a drug containing acetaminophen based on the data from the FDA. In addition, reports of death associated with acetaminophen have been increasing faster than those for aspirin, ibuprofen, and many other common over-the-counter pain medicines. 

In addition to Tylenol, non-steroidal antiinflammatory drugs, often referred to as NSAIDs, are very commonly used in chronic pain and are assumed to be well tolerated when used on a long-term basis for chronic pain. These include not only prescription drugs, but also over-the-counter drugs such as Advil, Aleve, and multiple other combinations. The chronic use of NSAIDs leads to multiple gastrointestinal, cardiovascular, renal complications, and hearing loss. 

- An estimated 60 million Americans regularly use NSAIDs, resulting in clinically significant upper gastrointestinal complications in up to 2% of users. Further, numerous lower gastrointestinal complications also have been reported.
- Gastrointestinal hemorrhages due to NSAID use result in up to 120,000 hospital admissions annually.
- Estimates based on 1998 data, more than 16,500 persons die from NSAID-related gastrointestinal adverse events each year in the United States alone. Significant cardiovascular and renal complications have also been reported.
- It has been shown that more Americans are hospitalized from NSAID bleeding than all American war casualties.
  - In 2009, there were 16,500 deaths with 107,000 hospitalizations at a cost of $2 billion. The estimations have stayed the same from the data available from 1998 In the United States.
  - Since 1986, almost 300,000 deaths have been estimated secondary to NSAID use.
  - Based on conservative updated estimates, NSAID-related deaths have increased to over 20,000 or more per year in the United States in 2009, which may be reaching at least 22,000 per year in the United States compared to 17,000 opioid deaths and 100 Tylenol-related deaths.
- Deaths and serious patient outcomes from FDA-approved drugs was reported to be almost 82,000 deaths and 471,000 serious patient outcomes in 2010. The total number of deaths exceeded 450,000 from 2000 to 2010 and serious outcomes exceeded 2.8 million.
- The clinical results for anti-epileptic drugs’ efficacy in reducing pain were disappointing with only 7% to 11% of patients with fibromyalgia and 9% to 17% of patients with painful diabetic neuropathy reporting a 50% reduction in pain.
- With sales exceeding $3 billion in 2010 for pregabalin and $4 billion for gabapentin, and with both makers fined by the Department of Justice (DOJ) for the promotion of off-label uses among physicians, these findings are an eye opener. It appears that we may be using these drugs too frequently without proof of efficacy.
- Derived from Cochrane reviews and NICE guidelines, gabapentin and pregabalin are being prescribed freely. Pregabalin prescribing has increased 350% in 5 years to 2.7 million scripts. Likewise, gabapentin prescribing has increased 150% in 5 years with 3.5 million scripts. There is also increasing published evidence concerning the abuse of pregabalin and gabapentin. Thus, these drugs may be used for many other purposes, such as euphoria. Pregabalin can be responsible for significant weight gain. Further, while studies have been published in prestigious journals, the majority of the publications published on these drugs appear to be industry sponsored.
- All these data show that any catastrophic complications secondary to epidural injections may be miniscule compared to all other complications.

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Further, the recent manuscript presented at the International Spine Intervention Society’s (ISIS) 22nd annual meeting in Orlando, Florida\(^\text{15}\) in a large investigation of 26,151 procedures, less than 0.1% of the procedures resulted in a transient complication requiring an emergency admission or an aborted procedure. This was a multicenter study; however, they also state that they followed ISIS guidelines. No one is certain what ISIS guidelines are, which sometimes result in a higher complication rate than lower complication rate. Even then, the complication rate, specifically with lumbar transforaminal epidural injections, is less than 0.1% which resulted in stopping the procedures and admitting the patients. The study was performed at three locations: the Department of Radiology, Mayo Clinic, in Rochester, Minn.; the Rehabilitation Institute of Chicago (RIC), Northwestern Memorial Hospital; and the Department of Physical Medicine and Rehabilitation, Penn Spine Center, University of Pennsylvania, in Philadelphia. In over 50,000 procedures in our practice, there has not been one admission due to procedure complications.