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# AAPM Response to Citizen's Petition of the FDA on Ultra High Dose Opioids

Comments from the American Academy of Pain Medicine

Docket no: FDA-2017-P-5396

Thank you for the opportunity to provide comments in response to the citizen's petition requesting that the FDA immediately seek removal of oral and transmucosal UHDU opioid analgesics from the market.

The American Academy of Pain Medicine (AAPM) appreciates the concerns of the petitioners for national health and safety; however, it opposes this petition on the grounds that it is predicated on an undefined concept, and several of its underlying premises are either false, misleading, or speculative. Therefore, its recommendations would, if implemented, be harmful to a large number of patients.

Specific false, misleading or speculative statements:

(1) It is true that the risks of chronic opioid therapy are in part proportional to dosage, and that there is a dearth of evidence supporting (or disputing) the benefits of long term use. However, the authors state that "CDC's expert consensus was that increasing dosages to 50 or more MME/day increases overdose risk without necessarily adding benefits for pain control or function." In fact, CDC articulated no such conclusion, but noted the problem of an inadequate evidence base for the benefits of long term use. The guidelines were directed only toward the use of chronic opioids for analgesia in primary care and do not address prolonged high dose therapy in specialized pain therapy, cancer-related pain, or the treatment of opioid use disorder.

(2) The statement that this Academy had "explicitly endorsed" the "notion that opioids should be prescribed without an upper limit," is false. The 20-year-old statement only noted that, "for most opioids, there does not appear to be an *arbitrary* upper dosage limit." (italics added for emphasis)

(3) They seek the removal of "ultra-high dosage unit (UHDU)" opioid formulations from the market; however, there is no accepted definition of this term, which appears to be a creation of the authors. They inexplicably limit the scope of their request to oral and transmucosal products, excluding transdermal medications, further demonstrating the idiosyncratic nature of their concept.

(4) The authors acknowledge that there is no relevant data, yet state, "… it is likely that morbidity and mortality was greater in cases involving UHDU opioids." This is entirely speculative. The assumption that children are less likely to suffer mortality based on the dose of the pill is misleading as even low

dose pills can cause respiratory arrest in children. The assumption that children are less likely to ingest several lower-dose pills than a single higher-dose one is also a guess. Limiting inadvertent exposure to opioids by reducing overreliance on opioid therapy through provider and patient education, while increasing the availability of interdisciplinary care for chronic pain patients are critical endeavors to safeguard our society. However, when appropriate indications exist for chronic opioid therapy, inadvertent exposures should be addressed by security measures and emergent at-home-treatment options such as naloxone, not dosage manipulations.

General Concerns: The petition relies upon the concept of morphine milligram equivalent (MME) daily doses. This idea, that a particular dose of one opioid is equivalent to a calculable dose of another, is useful at times as a gross approximation to guide transitions among opioids; however, it ignores the fact that opioids have different pharmacokinetics in different people, different pharmacodynamics related to opioid receptors that vary from person to person, and diverse interactions with drugs and foods. It ignores the rather obvious fact that a drug that acts within 20 minutes and is metabolized within 4 hours has no equivalent dose of a drug that acts in an hour and lasts for 24. It is, at best, a procrustean bed into which only a few fit well. Finally, the concept begs the question, equivalent in what way – equal analgesia, equal constipation, equal respiratory depression?

The petition ignores as well the needs of those being treated for opioid use disorder; which is a national epidemic that cannot be ignored. A typical daily dose of 16 mg sublingual buprenorphine would (using the low reliability MME concept) constitute 288 MME. Would patients be expected to take 6 smaller and costly doses?

Perhaps the most serious problem with the petition is its cavalier assumption that in those patients in whom high doses are required, the change would be "unlikely to result in a significant inconvenience or hardship." Nothing could be farther from the truth. It is undisputed that many end-of-life patients require and benefit from opioid doses that are often quite high. The exigencies of third-party payment are such that prescriptions for large pill quantities are routinely denied or subject to onerous authorization requirements. Thus in fact, the petition would deny analgesia to dying patients. This denial would also apply to the admittedly few patients with chronic noncancer pain who benefit from high doses. Further, if opioid dose per dispensed unit is lowered while the number of units dispensed is kept constant or reduced, then more frequent office visits to receive prescriptions will be required. This change, besides the inconvenience and cost of travel (often including parking fees), will increase the cost of care for patients on stable opioid doses due to their having a co-pay for each visit.

In summary, the petition has little to recommend it and much to suggest that its implementation would be harmful to the nation's health. For these reasons, we oppose it.

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## About AAPM

The American Academy of Pain Medicine is the premier medical association for pain physicians and their treatment teams with some 2,000 members. Now in its 34th year of service, the Academy's mission is to optimize the health of patients in pain and eliminate pain as a major public health problem by advancing the practice and specialty of pain medicine through education, training, advocacy and research. Information is available on the Academy's website at www.painmed.org.

*Approved by the AAPM Executive Committee on November 2, 2017*