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POSITION STATEMENT

ACMT Position Statement: Safety Issues Regarding Prescription Fentanyl Products

American College of Medical Toxicology [1]

Keywords Fentanyl · Opioid · Toxicology · Position statement · Transmucosal

This position statement addresses several specific areas regarding the safety of transdermal and transmucosal fentanyl.

The position of the American College of Medical Toxicology (ACMT) is as follows:

> *Fentanyl products must be prescribed with caution. Outpatient fentanyl products, including transmucosal and transdermal (patch) forms, should only be prescribed to patients with uncontrolled chronic pain and opioid tolerance. ACMT supports the FDA's decision to require a Risk Evaluation and Mitigation Strategy (REMS) for transmucosal immediate-release fentanyl (TIRF) products. Transmucosal fentanyl products should be prescribed at the lowest possible dose. Patients should be educated on the appropriate use, safe storage and disposal, and the risks associated with misuse of fentanyl products.*

While individual practitioners may differ, these are the positions of the ACMT at the time written, after a review of the issue and pertinent literature.

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Use of Prescription Fentanyl Products

Though primarily used intravenously in inpatient settings, fentanyl is available in a variety of formulations for outpatient chronic pain treatment. Fentanyl is commonly prescribed as a transdermal patch intended to administer the drug at a fixed hourly rate. It may also be used in a transmucosal form for rapid relief of pain, typically breakthrough pain in patients with malignancy-related pain. Similar to other prescription opioids, medical complications related to fentanyl have increased as fentanyl availability has expanded [1].

Toxicity from the use of a fentanyl transdermal patch can result through several distinct means. For example, patients and healthcare providers may inappropriately use fentanyl patches for acute pain management. This indication is not appropriate because upon initial application of a fentanyl transdermal patch, therapeutic drug concentrations may not be achieved for approximately 12 h or more. Substantial pharmacokinetic variability exists between individuals [2]. Therefore, a patient could potentially apply multiple patches due to a perceived lack of efficacy initially, with excessive drug delivery occurring hours later. Furthermore, given its high potency, transdermal fentanyl use is also recommended only in patients who are previously tolerant to opioids and require continuous (round-the-clock) opioid analgesic administration [1]. Hence, initiation of therapy in a non-tolerant individual increases the risk of toxicity. Additionally, drug delivery can be facilitated through several means, including increases in surface skin temperature or extracting the fentanyl from the transdermal patch. In experimental volunteer studies, heating fentanyl patches to 41 °C increased the rate of initial drug absorption and shortened the time to steady state serum concentrations [3]. Fentanyl overdose has been reported with inadvertent placement of a heating

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pad over a 75 μg/h patch [4]. Since the stratum corneum represents the primary barrier to transdermal absorption, placement of patches onto non-intact skin or onto mucosal surfaces can lead to dramatically increased absorption rates [5]. The clinician should thoroughly examine the opioid-poisoned patient in search of patches. In a case series of deaths involving fentanyl, 45 % of cases involved routes of exposure other than transdermal application; oral exposure accounted for the largest fraction of non-dermal routes [6]. Fentanyl's formulation as a transdermal patch also raises unique safety issues surrounding its disposal after use. Patches can contain a total of 1.25 to 10 mg of fentanyl with up to 82 % of drug remaining after normal therapeutic application [1]. Proper disposal of a used patch involves folding the adhesive surface together and then flushing it down a toilet. Failure to follow these procedures leaves the possibility of misuse or inadvertent pediatric exposures. The U.S. Food and Drug Administration's (FDA) advisory concerning the safe use of fentanyl patches includes information regarding appropriate patient and physician education, limiting use to opioid tolerant patients, and avoiding heating a patch once applied [7].

Fentanyl is also available in immediately active transmucosal formulations, including oral lozenges and buccal tablets, sublingual sprays, and films. These transmucosal formulations have mainly been studied in the treatment of breakthrough pain in patients with chronic pain who are maintained on opioids, primarily cancer patients [8–10]. In clinical studies, these formulations appear to be efficacious with low incidence of severe toxicity. However, there are limited data on adverse events outside of controlled studies. The FDA has released a safety advisory concerning fentanyl buccal tablets due to reports of adverse events [11].

The U.S. Food and Drug Administration has implemented the *Transmucoal Immediate Release Fentanyl* (*TIRF*) *Risk Evaluation and Mitigation Strategy* (*REMS*) *for use with transmucosal fentanyl formulations* [12]. Under this program, only certified prescribers may prescribe transmucosal fentanyl products outside of the hospital. Certification involves enrollment in an access program which consists of training, a knowledge assessment, and signed prescriber agreement. According to the REMS, these products should be prescribed only to opioid-tolerant cancer patients with chronic pain resistant to other therapies. To minimize risk of adverse events, patients should be started on the lowest possible dose, unless there is product-specific dose conversion information available.

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Compliance With Ethical Standards

Conflicts of Interest None.

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