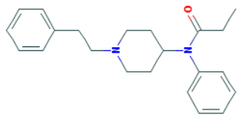
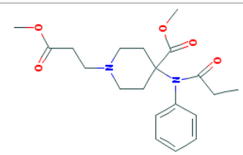
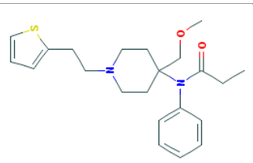
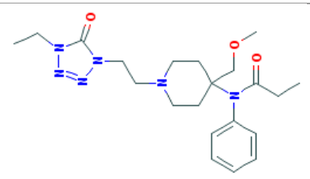
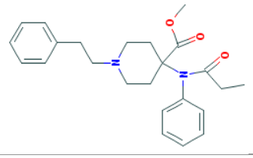
Table 1: Characteristics of Pharmaceutical Fentanyl and its Derivatives

Available at http://paindr.com/wpcontent/uploads/2018/05/2018_Combined-Characteristics-of-Illicit-Licit-Fentanyl-Derivatives.pdf

	Molecular Structure	Metabolism	Pharmaceutical Products	FDA Approved Indications[A]
Fentanyl/Fentanyl Citrate[1]		CYP3A4-mediated oxidative N-dealkylation to norfentanyl (inactive)	**Duragesic:** - Transdermal **Sublimaze:** - Injection (IV or IM) **TIRFs (fentanyl):** - Abstral sublingual tablet - Onsolis buccal soluble film - Subsys sublingual spray **TIRFs (fentanyl citrate):** - Actiq oral lozenge - Fentora buccal tablet - Lazanda nasal spray	**Duragesic:** - Management of pain in opioid-tolerant patients, severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate **Sublimaze:** - Analgesic action of short duration during the anesthetic periods, premedication, induction and maintenance and in the immediate postoperative period (recovery room) as the need arises - Use as a narcotic analgesic supplement in general or regional anesthesia - Administration with a neuroleptic as an anesthetic premedication, for the induction of anesthesia and as an adjunct in the maintenance of general and regional anesthesia - Use as an anesthetic agent with oxygen in selected high-risk patients, such as those undergoing open heart surgery or certain complicated neurological or orthopedic procedures. **Actiq, Onsolis, Fentora, Abstral, Subsys, Lazanda:** - Management of breakthrough pain in patients with cancer, 18 years of age and older (16+ for Actiq), who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain
Remifentanil[2-5]		Hydrolysis by non-specific blood and tissue esterases to inactive remifentanil acid (carboxylic acid metabolite)	**Ultiva:** - Injection (IV only)	- Analgesic agent for use during the induction and maintenance of general anesthesia for inpatient and outpatient procedures - For continuation as an analgesic into the immediate postoperative period in adult patients under the direct supervision of an anesthesia practitioner in a postoperative anesthesia care unit or intensive care setting - Analgesic component of monitored anesthesia care in adult patients
Sufentanil[1]		CYP3A4-mediated O-demethylation to methylsufentanil (10% pharmaceutical activity as sufentanil)	**Sufentanil Citrate:** - Injection (IV and epidural)	- Analgesic adjunct in the maintenance of balanced general anesthesia in patients who are intubated and ventilated - Primary anesthetic agent for the induction and maintenance of anesthesia with 100% oxygen in patients undergoing major surgical procedures, in patients who are intubated and ventilated - For epidural administration as an analgesic for labor and delivery
Alfentanil[6]		CYP3A4-mediated piperidine N-dealkylation to noralfentanil (inactive) CYP3A5-mediated amide N-dealkylation to N-phenylpropionamide	**Rapifen:** - Injection (IV only)	- Analgesic adjunct given in incremental doses in the maintenance of anesthesia with barbiturate/nitrous oxide/oxygen - Analgesic administered by continuous infusion with nitrous oxide/oxygen in the maintenance of general anesthesia - Primary anesthetic agent for the induction of anesthesia in patients undergoing general surgery in which endotracheal intubation and mechanical ventilation are required - Analgesic component for monitored anesthesia care (MAC)
Carfentanil[7]		No human carfentanil metabolism data is available[B]	**Wildnil:**	- Used for chemical immobilization of free ranging and confined large mammals - Federal law restricts this drug to use by or on the order of a licensed veterinarian. The licensed veterinarian shall be a veterinarian engaged in zoo and exotic animal practice, wildlife management programs, or research

[A]All molecular structures were obtained from pubchem; [B]Notably, only fentanyl, remifentanil, sufentanil, and alfentanil have FDA approved indications in humans. However, all 5 chemicals are currently listed as schedule II by the DEA. [B]A study in human liver microsomes and human hepatocytes showed the production of 12 metabolites, with N-Dealkylation and monohydroxylation of the piperidine ring being the primary metabolism pathways[7]

Table developed by Nicholas Trotta, PharmD and edited by Jeffrey Bettinger, PharmD.
Reviewed for accuracy and posted by Jeffrey Fudin, PharmD, DAIPM, FCCP, FASHP, FFSMB

References for Characteristics of Pharmaceutical Fentanyl and its Derivatives:

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5. Westmoreland CL, Hoke JF, Sebel PS, Hug CC, Muir KT. Pharmacokinetics of remifentanil (GI87084B) and its major metabolite (GI90291) in patients undergoing elective inpatient surgery. Anesthesiology 1993; 79:893-903
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Table 2: Pharmacokinetic and Pharmacodynamic Properties of Pharmaceutical Fentanyl and its Derivatives[1-3]

	Route of Administration:	Percent Absorption (bioavailability)	Protein Binding	Terminal Half-Life	Antinociceptive Potency Ratio to Morphine	Antinociceptive Potency Compared to Fentanyl
Transdermal Fentanyl (Duragesic)	Transdermal	92%	80-85%	20-27 hours after patch removal	80-100	1
Fentanyl Citrate Injection	IV or IM	100%	80-85%	2-4 hours	80-100	1
TIRFs	Buccal: - Fentora (tablet) - Onsolis (film) Lozenge: - Actiq Nasal spray: - Lazanda Sublingual: - Abstral (tablet) - Subsys (spray)	Fentora: 65% Onsolis: 71% Actiq: 50% Lazanda: 89% Abstral: 54% Subsys: 76%	80-85%	Fentora: 2.6-11.7 hours Onsolis: 14 hours Actiq: 7 hours Lazanda: 15-25 hours Abstral: 5-14 hours Subsys: 5-12 hours	80-100	1
Remifentanil	IV only	100%	70%	3-10 minutes	100-200	1-2
Sufentanil	IV or epidural	100%	91-93%	~160 minutes	500-1000	5-10
Alfentanil	IV only	100%	92%	90-110 minutes	25	0.25
Carfentanil	IM in large mammals	N/a	N/a	~5.7 hours[16]	10000	100

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Reviewed for accuracy and posted by Jeffrey Fudin, PharmD, DAIPM, FCCP, FASHP, FFSMB

References:

1. Stanley TH. The history and development of the fentanyl series. J Pain Symptom Manage. 1992 Apr;7(3 Suppl):S3-7.
2. Elbaridi N, Kaye AD, Choi S, Urman RD. Current Concepts of Phenylpiperidine Derivatives Use in the Treatment of Acute and Chronic Pain. Pain Physician. 2017 Feb;20(2S):SE23-SE31.
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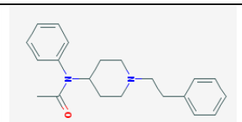
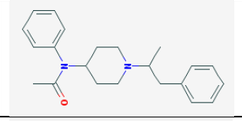
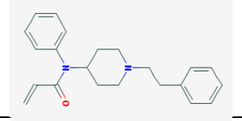
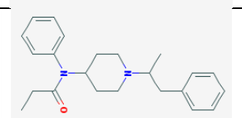
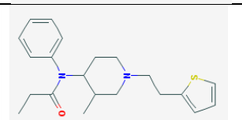
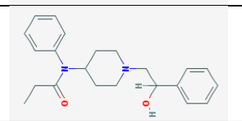
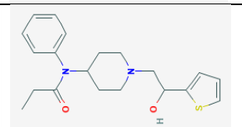
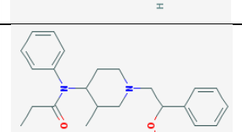
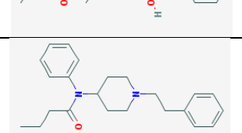
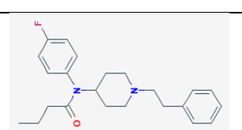
Table 3: Characteristics of Nonpharmaceutical Fentanyls Listed by DEA as Schedule 1 as of April, 2018

Chemical Name	Antinociceptive Potency Ratio to Morphine	Antinociceptive Potency Ratio to Fentanyl	Chemical Structure
Acetyl fentanyl[1,2]	15.7[A]	0.29[A]	
Acetyl alpha-methyl fentanyl[2]	3.1	0.06	
Acryl fentanyl OR acryloyl fentanyl[3,4]	169.5[A]	0.76[A]	
Alpha-methyl fentanyl[2]	56.9[A]	1.1[A]	
Alpha-methylthio fentanyl	N/a	N/a	
Beta-hydroxy fentanyl	N/a	N/a	
Beta-hydroxythio fentanyl	N/a	N/a	
Beta-hydroxy-3-methyl fentanyl or ohmefentanyl[5-6]	2957-6300[A]	13-28[A]	
Butyryl fentanyl[2]	7.0[A]	0.13[A]	
Cyclopentyl fentanyl	N/a	N/a	N/a (case report only)
Cyclopropyl fentanyl	N/a	N/a	N/a
4-chloroisobutyryl fentanyl OR parachloroisobutyryl fentanyl	N/a	N/a	N/a
4-fluorobutyr fentanyl OR parafluorobutyr fentanyl	N/a	N/a	

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[A]Antinociceptive potency ratio was calculated by comparing median effective dose (ED_{50}) values in mice after hot plate and/or writhing episode testing

[B]4-fluoroisobutyrylfentanyl, fentanyl, and morphine administered subcutaneously to mice producing increases in tail-flick latency in a tail withdrawal assay with ED_{50} values of 1.61mg/kg, 0.122mg/kg, and 12mg/kg, respectively

[C]Lofentanil potency ratio determined by comparing ED_{50} values in rats after hot plate testing after intrathecal injection of fentanyl, lofentanil, and morphine, respectively

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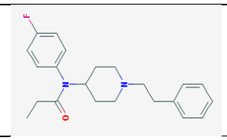
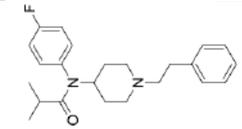
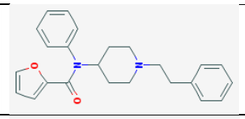
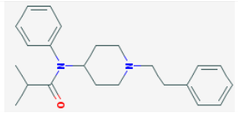
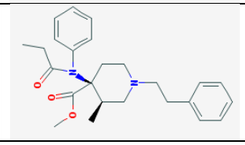
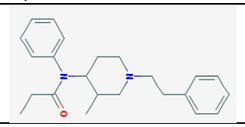
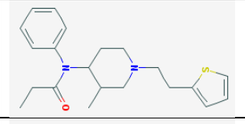
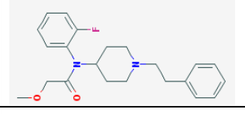
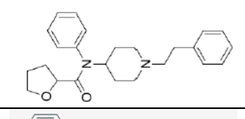
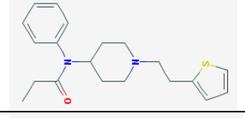
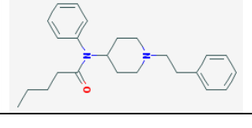
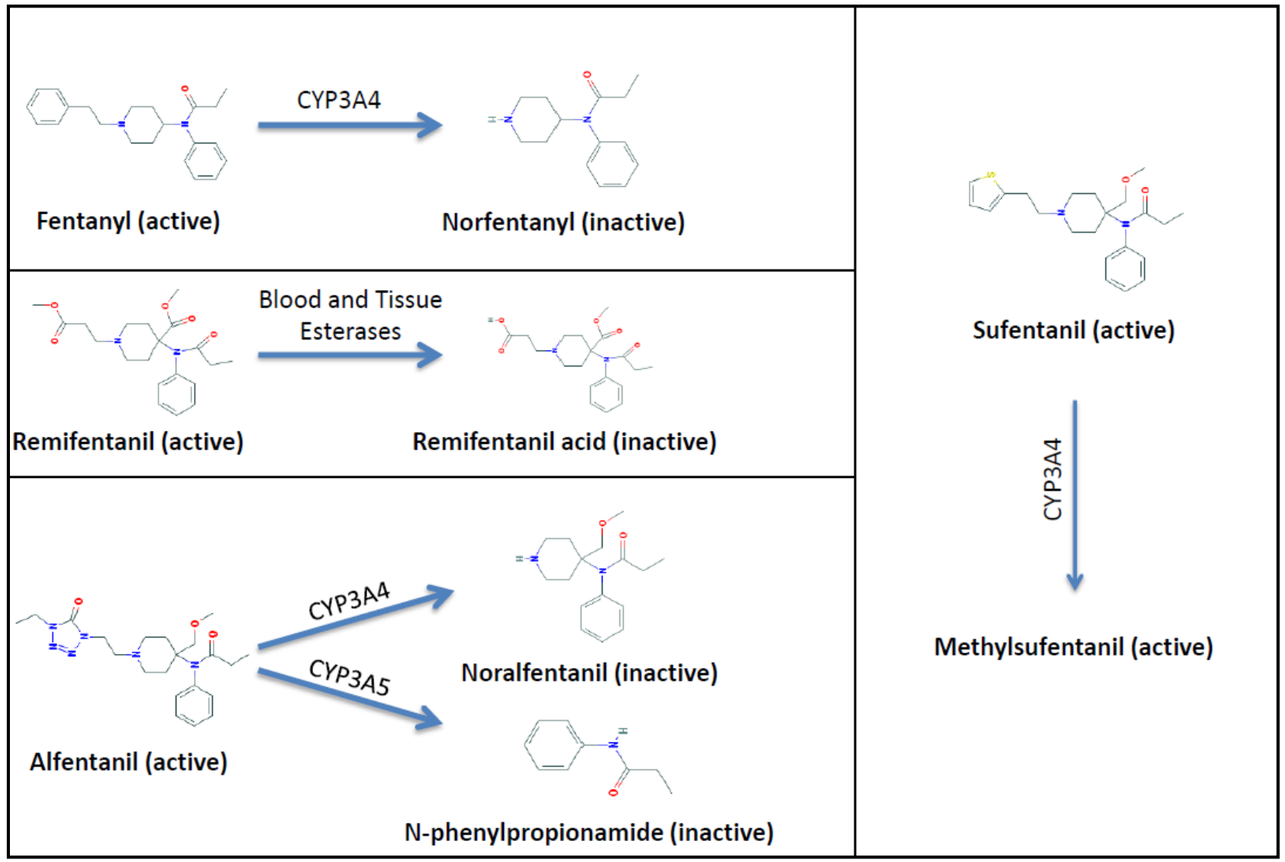
4-fluoro fentanyl OR parafluoro fentanyl[2]	15.7[A]	0.29[A]	
4-fluoroisobutyryl fentanyl OR para-fluoroisobutyryl fentanyl[7]	57[B]	0.08[B]	
Furanyl fentanyl[8]	N/a	N/a	
Isobutyryl fentanyl[2]	1.3-6.9[A]	0.02-0.13[A]	
Lofentanil[9]	210[C]	70[C]	
4-methoxybutyryl fentanyl OR para-methoxybutyryl fentanyl	N/a	N/a	N/a
Methoxyacetyl fentanyl	N/a	N/a	N/a
3-methyl fentanyl[2]	48.5-569[A]	0.9-10.5[A]	
3-methylbutyryl fentanyl	N/a	N/a	N/a
3-methylthio fentanyl	N/a	N/a	
Ocfentanil[10,11]	200[11]	2.5[A]	
Tetrahydrofuranyl fentanyl[12]	N/a	N/a	
Thio fentanyl	N/a	N/a	
Valeryl fentanyl	N/a	N/a	

Figure 1: Metabolic Pathways of Pharmaceutical Fentanyl and its Derivatives:



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