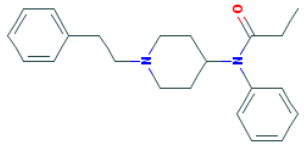
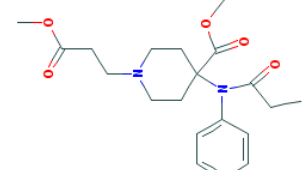
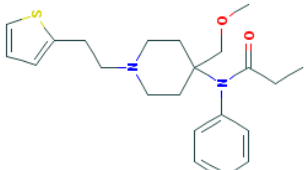
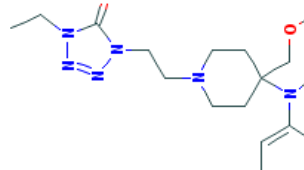
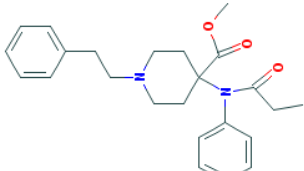


Table 1: Characteristics of Pharmaceutical Fentanyl and its Derivatives

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 Citrate¹		CYP3A4-mediated oxidative N-dealkylation to norfentanyl (inactive)	Duragesic: <ul style="list-style-type: none"> - Transdermal Sublimaze: <ul style="list-style-type: none"> - Injection (IV or IM) TIRFs (fentanyl): <ul style="list-style-type: none"> - Abstral sublingual tablet - Onsolis buccal soluble film - Subsys sublingual spray TIRFs (fentanyl citrate): <ul style="list-style-type: none"> - Actiq oral lozenge - Fentora buccal tablet - Lazanda nasal spray 	Duragesic: <ul style="list-style-type: none"> - 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: <ul style="list-style-type: none"> - 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: <ul style="list-style-type: none"> - 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
Remifentanyl²⁻⁵		Hydrolysis by non-specific blood and tissue esterases to inactive remifentanyl acid (carboxylic acid metabolite)	Ultiva: <ul style="list-style-type: none"> - Injection (IV only) 	<ul style="list-style-type: none"> - 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
Sufentanyl¹		CYP3A4-mediated O-demethylation to methylsufentanyl (10% pharmaceutical activity as sufentanyl)	Sufentanyl Citrate: <ul style="list-style-type: none"> - Injection (IV and epidural) 	<ul style="list-style-type: none"> - 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
Alfentanyl⁶		CYP3A4-mediated piperidine N-dealkylation to noralfentanyl (inactive) CYP3A5-mediated amide N-dealkylation to N-phenylpropionamide	Rapifen: <ul style="list-style-type: none"> - Injection (IV only) 	<ul style="list-style-type: none"> - 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)
Carfentanyl⁷		No human carfentanyl metabolism data is available ^B	Wildnil:	<ul style="list-style-type: none"> - 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

^AAll molecular structures were obtained from pubchem; ^BNotably, only fentanyl, remifentanyl, sufentanyl, and alfentanyl have FDA approved indications in humans. However, all 5 chemicals are currently listed as schedule II by the DEA. ^BA 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 pathways⁷

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

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Table 2: Pharmacokinetic and Pharmacodynamic Properties of Pharmaceutical Fentanyl and its Derivatives¹⁻³

	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
Remifentanyl	IV only	100%	70%	3-10 minutes	100-200	1-2
Sufentanyl	IV or epidural	100%	91-93%	~160 minutes	500-1000	5-10
Alfentanyl	IV only	100%	92%	90-110 minutes	25	0.25
Carfentanyl	IM in large mammals	N/a	N/a	~5.7 hours ¹⁶	10000	100

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:

1. Stanley TH. The history and development of the fentanyl series. J Pain Symptom Manage. 1992 Apr;7(3 Suppl):S3-7.
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Table 3: Characteristics of Nonpharmaceutical Fentanyls Listed by DEA as Schedule 1 as of April, 2018

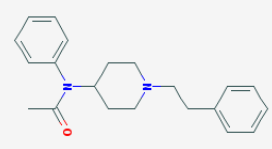
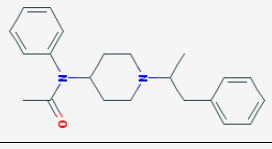
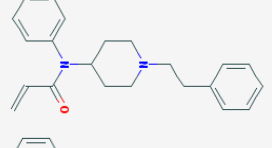
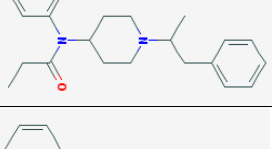
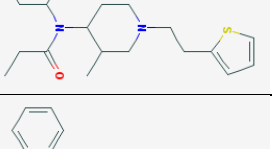
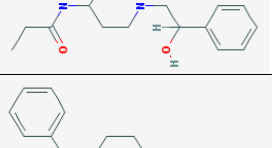

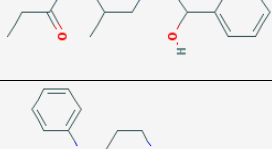
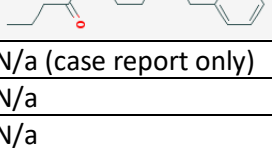
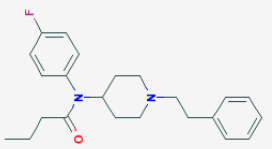
Chemical Name	Antinociceptive Potency Ratio to Morphine	Antinociceptive Potency Ratio to Fentanyl	Chemical Structure
Acetyl fentanyl ^{1,2}	15.7 ^A	0.29 ^A	
Acetyl alpha-methyl fentanyl ²	3.1	0.06	
Acryl fentanyl OR acryloyl fentanyl ^{3,4}	169.5 ^A	0.76 ^A	
Alpha-methyl fentanyl ²	56.9 ^A	1.1 ^A	
Alpha-methylthio 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-fluorobutyryl fentanyl OR parafluorobutyryl fentanyl	N/a	N/a	

Table developed by Jeffrey Bettinger, PharmD.

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

^AAntinociceptive potency ratio was calculated by comparing median effective dose (ED₅₀) values in mice after hot plate and/or writhing episode testing

^B4-fluoroisobutyrylfentanyl, fentanyl, and morphine administered subcutaneously to mice producing increases in tail-flick latency in a tail withdrawal assay with ED₅₀ values of 1.61mg/kg, 0.122mg/kg, and 12mg/kg, respectively

^CLofentanil potency ratio determined by comparing ED₅₀ values in rats after hot plate testing after intrathecal injection of fentanyl, lofentanil, and morphine, respectively

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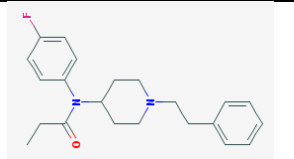
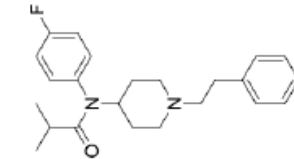
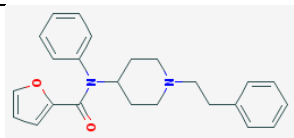
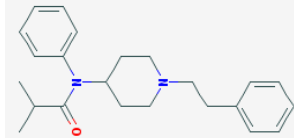
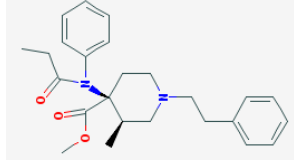
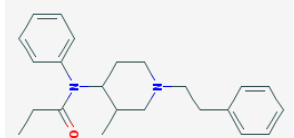
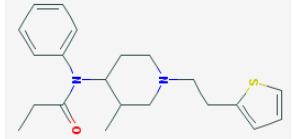
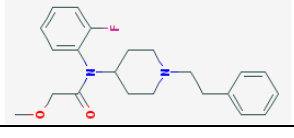
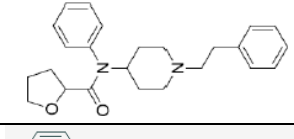
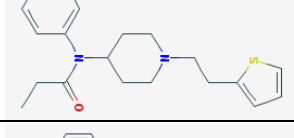
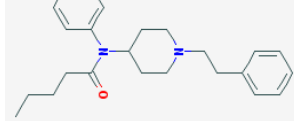
4-fluoro fentanyl OR parafluoro fentanyl ²	15.7 ^A	0.29 ^A	
4-fluoroisobutyryl fentanyl OR para-fluoroisobutyryl fentanyl ⁷	57 ^B	0.08 ^B	
Furanyl fentanyl ⁸	N/a	N/a	
Isobutyryl fentanyl ²	1.3-6.9 ^A	0.02-0.13 ^A	
Lofentanil ⁹	210 ^C	70 ^C	
4-methoxybutyryl fentanyl OR para-methoxybutyryl fentanyl	N/a	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:

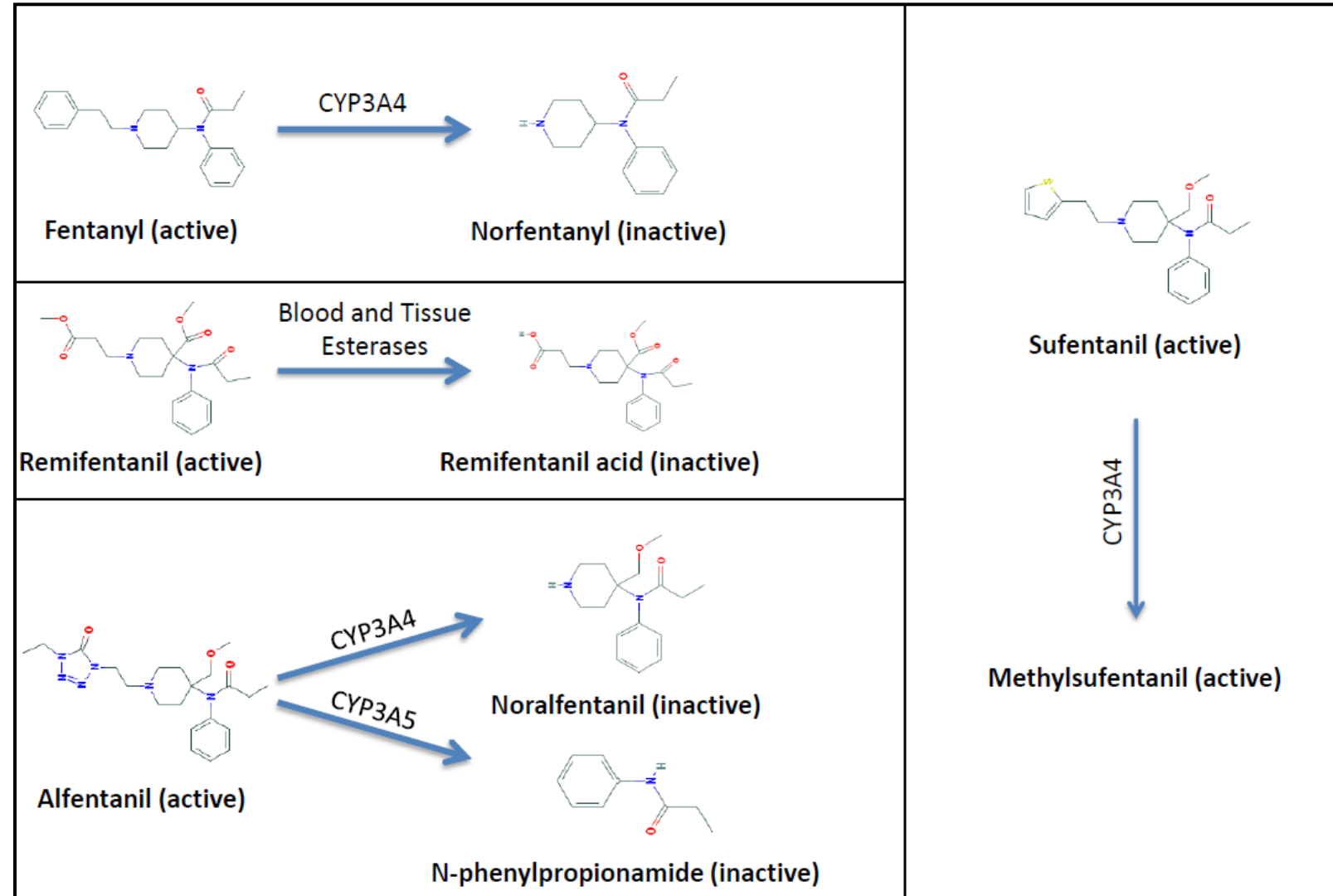


Table developed by Nicholas Trotta, PharmD and Jeffrey Bettinger, PharmD.

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