

# Opioids — Effects on Human Performance and Behavior

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# Opioids — Effects on Human Performance and Behavior<sup>a</sup>

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**ABSTRACT:** The purpose of the monograph is to provide readers with a summary of the literature relating selected opioids to performance issues, specifically driving. This monograph provides a summary of information to aid expert witnesses in preparing for court testimony. Information for codeine, hydrocodone, hydromorphone, methadone, morphine, and oxycodone is provided. In addition to a review of performance studies, a summary of acute and chronic pharmacology, pharmacokinetics, and metabolism is included. Opioids appear to impair psychomotor functioning likely to be important to the performance of complex, divided attention tasks such as driving. This impairment is notably more prevalent in individuals with no history of opioid use; individuals with long-term opioid use do not demonstrate as extensive of an impairment. Other factors such as personality, environment, and pain control also sharply modulate opioid impairment.

**KEY WORDS:** Codeine, driving under the influence of opioids, hydrocodone, hydromorphone, methadone, morphine, opioids, oxycodone, performance testing.

## INTRODUCTION

### History

Opioids are naturally occurring alkaloid analgesics derived from the opium poppy *Papaver somniferum*. Typically, the seedpods are scored and the milky exudate contains morphine, codeine, and numerous other alkaloids such as papaverine and thebaine. Natural opioids, including opium, tincture of opium, and paregoric, have been used as analgesics or drugs of abuse for centuries. There is evidence of the use of opium in the Sumerian culture as early as 3500 BCE, and the writings of Theophrastus around 200 BCE describe the use of opium in Greek medicine.

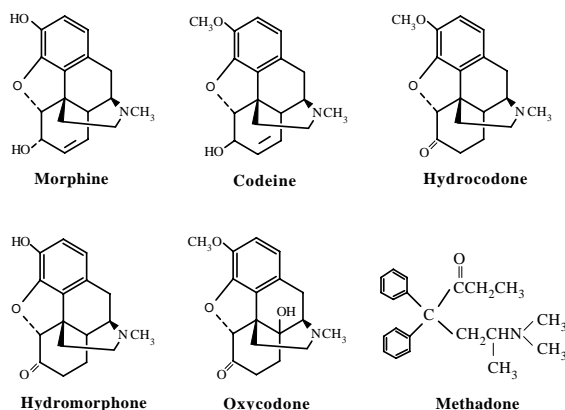
In the 1800s and 1900s, synthetic and semi-synthetic derivatives of morphine and codeine were developed in an effort to increase the potency of analgesia and reduce undesirable side effects. Diacetylmorphine was synthesized in 1874 and introduced as a nonaddicting, analgesic, antitussive, and antidiarrheal in 1898. The opioid drug class includes numerous compounds that are structurally related to morphine and numerous compounds that are pharmacologically related, but structurally unrelated.

A wide range of opioids has been isolated from opium and a wide range of both structurally and pharmacologically related compounds has been synthesized. **Table 1** includes a list of opioids and their synonyms. Though not all of the compounds listed in Table 1 are covered in this

review, this table indicates the large number of compounds that have opioid actions. **Structure 1** includes the molecular structures of codeine, hydrocodone, hydromorphone, methadone, morphine, and oxycodone, which are the drugs covered in this review. These drugs were selected based on their prevalence in drug-impaired driving cases and their higher frequency of use in the medical and drug abuse communities. All of these compounds have varying degrees of antinociceptive, antitussive, and antidiarrheal effects. Additionally, all the compounds have varying impairing effects and abuse potential.

### Modes of Action

A great deal of work has been done over the past decades regarding the modes of action of opioids. Great emphasis has been placed on developing effective antinociceptive drugs that reduce the classic side effects of



**Structure 1.** Structures of the compounds discussed.

<sup>a</sup>The opinions expressed in this paper reflect those of the authors and are not to be construed as an official position of the Department of Navy, Department of Defense, or the State of Colorado.

**Table 1.** Opiate drugs (synthetic and natural) — Mode of action, serum half-life, and metabolites<sup>a</sup>

Drug	Synonym	Mode of action	T <sub>1/2</sub> (h)	Metabolites
Acetylmethadol	LAAM, ORLAAM	μ-Agonist	32–116	Acetylmethadol, noracetylmethadol, dinoracetylmethadol, methadol
Alfentanil	Alfenta, Rapifen	μ-Agonist (short acting)	1–2	Noralfentanil, <i>O</i> -demethylnoralfentanil (conjugated)
Buprenorphine	Buprenex	μ-Agonist, κ-antagonist	3.5	Norbuprenorphine, buprenorphine (conjugated)
Butorphanol	Stadol	κ-Agonist, μ-antagonist	3–8	3-Hydroxybutorphanol, norbutorphanol (conjugated)
Codeine	Generic preps	μ-Agonist	3	Codeine, morphine, norcodeine (conjugated)
Dextromoramide	Palfium, Jetrium	μ-Agonist	1.5–4.7	Dextromoramide
Dezocine	Dalgan	μ-Agonist, δ-antagonist	2.6–2.8	Glucuronide conjugate
Dihydrocodeine	Drocode, DHCPlus	μ-Agonist	3–5	Morphine
Etorphine	Oripavine	μ-Agonist	— <sup>b</sup>	Etorphine-3-glucuronide (rat)
Fentanyl	Sublimaze	μ-Agonist (short acting)	37	Despropionylfentanyl, norfentanyl, hydroxyfentanyl, hydroxynorfentanyl
Heroin	None	μ-Agonist	Minutes	6-Acetylmorphine, morphine, normorphine (conjugated)
Hydrocodone	Lortab, Vicodin	μ-Agonist	3–9	Norhydrocodone, hydromorphone, hydrocodol, hydromorphol (conjugated)
Hydromorphone	Dilaudid	μ-Agonist	1–4	Hydromorphol (conjugated)
Ketobemidone	Cliradon, Ketogin	μ-Agonist	1.8–4.2	Norketobemidone, ketobemidone, 4-hydroxyketobemidone
Levorphanol	Dromoran	μ-Agonist (long acting)	12–16	Norlevorphanol
Meperidine	Pethidine, Demerol	μ-Agonist (long acting)	2–4	Normeperidine, meperidinic acid, normeperidinic acid
Meptazinol	Meptid	μ <sub>1</sub> -Agonist	2	Meptazinol (conjugated)
Methadone	Physeptone, Dolophine	μ-Agonist (long acting)	15–55	Methadol, normethadol, EDDP, EMDP (conjugated)
Morphine	Generic preps	μ-Agonist	3	Morphine, normorphine (conjugated)
Nalbuphine	Nubain	μ-Antagonist, κ-agonist	2–8	Nalbuphine, nornalbuphine (conjugated)
Oxycodone	Roxidone, Percocet, Percodan	μ-Agonist	4–6	Noroxycodone, oxymorphone (conjugated)
Oxymorphone	Numorphan	μ-Agonist	3–4	6-Oxymorphol, oxymorphone (conjugated)
Papveretum <sup>c</sup>	Omnopon	μ-Agonist (long acting)	3	Morphine and codeine metabolites
Pentazocine	Talwin	Mixed κ-, μ-, δ-agonist	2–4	Pentazocine, <i>cis</i> - and <i>trans</i> -hydroxypentazocine, <i>trans</i> -carboxypentazocine
Propoxyphene	Darvon, Dolene	μ-Agonist	8–24	Norpropoxyphene, dinorpropoxyphene, cyclic dinorpropoxyphene
Sufentanil	Sufenta	μ-Agonist (short acting)	1.6–5.7	<i>O</i> -Desmethylsufentanil, <i>N</i> -desalkylsufentanil
Tilidine	Valoron	μ-Agonist	3.3–4.9	Nortilidine, bisnortilidine
Tramadol	Ultram	μ-Agonist	4–7	Nortramadol, dinortramadol, <i>O</i> -desmethyltramadol, <i>O</i> -desmethylnortramadol, <i>O</i> -desmethylidinortramadol (conjugated)

<sup>a</sup> Adapted from [12,60,71,124].

<sup>b</sup> No estimate is available.

<sup>c</sup> Mixed morphine and alkaloids.

opioids (dry mouth, drowsiness, nausea, respiratory depression, constipation) and also reduce the abuse and addiction potential. To this end, much has been studied about the mechanisms by which opioids potentiate pain and affect the brain.

Three primary groups of opioid receptors have been described: mu, kappa, and delta (μ, κ, δ) [79,140]. These receptor classes also have several sub-classes described. All of the receptors have endogenous ligands known as

enkephalins and endorphins. All of these receptors are found in brain and spinal cord tissue. This system of receptors and endogenous ligands appears to be intimately involved with natural modulation of pain in the body.

Signal transduction mechanisms have been described for each of the classes of receptors. The μ and δ receptors are G<sub>i</sub> protein linked to the inhibition of adenylyl cyclase activity. Thus, binding at the μ and δ receptors will result in reduced cyclic adenosine monophosphate (cAMP) pro-

duction and a resultant increase in intracellular potassium concentration and hyperpolarization of the cell membrane [202]. Two subdivisions of  $\mu$  receptors,  $\mu_1$  and  $\mu_2$ , are thought to have a greater role in the modulation of pain and respiratory depression, respectively [71].

The  $\kappa$  receptors have an apparent  $G_i$  protein link to calcium channels [46]. Agonists of these receptors produce analgesia, diuresis, sedation, and dysphoria without strong respiratory depression and constipation observed with  $\mu$  agonists [246]. The  $\delta$  receptors are not well described though endogenous ligand binding may predominate at this receptor class.

Table 1 presents a summary of the modes of action of a variety of opioid drugs. Most of the opioids that are widely used are either morphine-like  $\mu$  receptor agonists or partial agonist-antagonists at  $\mu$  and  $\kappa$  receptors [246]. It is as yet unclear if a highly selective agonist or antagonist of any receptor could produce efficient analgesia without deleterious side effects. **Table 2** presents a summary of pharmacological effects by opioid receptor.

#### Analysis Methods

**Body Fluids Extraction and Derivatization.** As with most opioid analyses, screening technologies as well as confirmatory technologies are widely used. Thin layer chromatography (TLC) can be used to detect a wide variety of opioid drugs. Immunoassay-based screening technologies such as enzyme multiplied immunoassay technique (EMIT; Dade-Behring Diagnostics), kinetic interaction of micro particles in solution (KIMS; Roche

Diagnostics), fluorescence polarization immunoassay (FPIA; Abbott Diagnostics), and cloned enzyme donor immunoassay (CEDIA; Microgenics) all offer varying cross reactivity to the morphine-like compounds. All of these kits can be used on blood, urine, or other matrices. However, blood analyses usually require additional preparation of the samples (precipitation of protein or extraction) and often fall outside of the manufacturer's specifications on the kits. More assays are becoming available for the screening of non-morphine like opioid drugs.

A wide variety of confirmatory testing methods, predominantly gas chromatography/mass spectrometry (GC/MS), are used. New methods using high performance liquid chromatography mass spectrometry are being developed [1,8,10,21,23,25,31,38,41,69,75,83,103,116,126,160,169,177,189,191,203,213,227]. As many of the compounds are present in both blood and urine as conjugates, hydrolysis of these conjugates is often necessary prior to extraction. Hydrolysis is often accomplished by the addition of strong acid and pressurized heat treatment or the addition of  $\beta$ -glucuronidase. Acid hydrolysis is faster; however, compounds such as 6-acetyl-morphine are not stable under these conditions. Enzymatic hydrolysis occurs under gentler conditions, but usually takes longer. Additionally, enzyme sources are usually derived from bacteria and have varying degrees of effectiveness in hydrolyzing the conjugates of interest.

Confirmation testing usually requires the extraction of compounds from the biological matrix either by solid phase extraction (SPE) or liquid-liquid extraction. A wide range of methods has been reported for primarily cationic and mixed bed type SPE methods. Liquid-liquid extractions classically use an initial basic extraction into an organic solvent followed by subsequent acidic back extraction clean up steps and final extraction into an organic solvent.

For GC/MS, derivitization is often necessary for acceptable chromatographic performance and fragmentation. Sylation with agents such as *bis*-(trimethylsilyl) trifluoroacetamide (BSTFA), and acylation with agents such as propionic anhydride, pentafluoropropionic anhydride are common means of derivitization. Care should be exercised if derivitizing with acetic anhydride, understanding that diacetylmorphine will be formed from 6-acetyl morphine and morphine present in the sample. If the analysis needs to maintain this information, deuterated acetic anhydride is available so that diacetylmorphine formed during derivitization can be distinguished as can the derivitized 6-acetyl morphine from morphine.

A wide range of sensitivities are obtained by various methods and the specific limits of detection and linearity pertinent to the individual analysis should be considered in any interpretation.

**Table 2.** Summary of opioid pharmacological effects

Opioid receptor	Pharmacological effect
$\mu$ ( $\mu$ )	Analgesia — Supraspinal Respiratory depression Miosis Euphoria Decreased gastrointestinal activity Drowsiness Nausea, vomiting Changes in body temperature Mental clouding Tolerance Increased addiction potential
$\kappa$ ( $\kappa$ )	Analgesia — Spinal Diuresis Sedation Dysphoria Mild respiratory depression Miosis Reduced addiction potential
$\delta$ ( $\delta$ )	Analgesia Dysphoria Delusions Hallucinations

**Alternate Matrices.** In the case of hair analysis, an additional step to digest the hair matrix is required. Typically this is accomplished by the addition of strong base, strong acid, enzymes, or sodium sulfide. These conditions result in varying degrees of digestion of the hair matrix and do not completely digest melanosomes present in the hair. This may result in the incomplete liberation of the target compounds from the hair (especially in the case of enzymatic digestion) for extraction and analysis [33]. Likewise, the relative impermeability of melanosomes to digestion may result in the sequestration of target compounds in melanosomes. As much of the stored drug in hair may be associated with melanin even as a covalent adduct, this sequestration may dramatically reduce the sensitivity of the testing [32,33,209].

Even with the potential difficulties in use of hair, many opioids have been reported as detected in hair [212,213]. The biology of hair growth and the potential for surface contamination have confounded the relation of hair concentrations to serum concentrations. Additionally, hair concentrations may saturate at relatively low concentrations for many drugs and even for some opioids [209].

Saliva has also become a novel alternative testing method that may help provide rapid roadside drug testing results. Many compounds have been detected in saliva. Screening and confirmatory technologies typical of other matrices are also used in saliva testing. Confounding the

relationship of saliva concentrations to serum levels is the potential for oral contamination.

Other matrices such as fingernails, sweat, breastmilk, and sebum have all been examined for their content of various opioids. Most of these analyses are again conducted by immunoassays and GC/MS or LC/MS methods. Depending on the matrix, additional steps may be necessary to break down the matrix to facilitate extraction.

## I. CODEINE

One of the most extensively used opioids, codeine is used in the management of mild to moderate pain and as an antitussive. Codeine is a mixed agonist/antagonist of  $\mu$  and  $\delta$  receptors. It is produced both commercially from morphine and is a natural component of opium. Single oral dosages range from 15–60 mg with total daily dosages typically from 60–240 mg. Codeine is available in numerous formulations and is indicated for analgesia and as an antitussive. Preparations include tablets, syrups, and solutions for subcutaneous injection.

### A. Pharmacology and Pharmacokinetics

Following oral dosage, approximately 10–20% is excreted in the urine within 24 h [177]. Three days after codeine use, only morphine was present in urine and was identical to morphine or heroin use [177]. Ninety-five percent of a single dose was eliminated in 48 h [13].

**Table 3.** Overview of controlled administration studies of codeine with psychomotor and cognitive effects

Drug	Dose	Study group <sup>a</sup>	End point measured <sup>b</sup>	Effects <sup>b</sup>	Ref.
Codeine	0, 30, 60, 90 mg orally	0/6; NU	DVA, CRT, CFF, VMC; 0.75–2 h	Linear dose dependent decrease in VMC and DVA performance	[22]
Codeine	0, 32 mg at increasing altitudes	16/0; NU	DSST	Impaired performance at 2,000 ft, improved performance above 11,000 ft	[63]
Codeine	0, 60, 120 mg orally	42/6; U	DRE assessment	DRE evaluation criteria could, with mixed results predict acute administration of codeine	[97]
Codeine	25 mg orally	90/0; NU	DS; 30 min	Reduced tachycardia induced by emergency situations; impairment of steering direction, flashing lights, brakes, clutch	[138]
Codeine $\pm$ ethanol	0, 50 mg orally; 50 mg orally + 0.5 gm/kg ethanol	70/0; NU	DS; 30 min	Increased risk for both codeine and ethanol in monotonous and emergency driving	[137]
Codeine $\pm$ diazepam	0, 100 mg orally	5/5; NU	Body sway, DSST, VAS, CFF, MW, PHYS; 1.5 h	No performance impairment; codeine reduced the absorption of diazepam; plasma concentrations: 1.5 h = 105, 3 h = 93, 4.5 h = 78 ng/ml	[196]
Morphine, codeine	0, 20, 40 mg morphine; 0, 60, 120 mg codeine orally	9/3; NU	Wartegg personality, ARCI, PHYS, MW, DSST; 0–4 h	Dose-related miosis at plasma levels of codeine 52–256 ng/mL, morphine 12–50 ng/ml; no impairment by codeine or morphine	[222]

<sup>a</sup> Number of subject studied: Male/female; NU: Non-user; U: User.

<sup>b</sup> DVA: Dynamic visual acuity; CRT: Complex reaction time; CFF: Critical Flicker Fusion; VMC: Visuomotor coordination test; DSST: Digital symbol substitution test; DRE: Drug recognition expert; DS: Driving simulator; VAS: Visual analog scale, rating of subjective effects; MW: Maddox-Wing Test; PHYS: Physiological testing (varied combination of heart rate, blood pressure, skin temperature, etc.); ARCI: Subject effect questionnaire.

The serum half-life for codeine is approximately 3 h. **Table 3** contains reported serum concentration ranges after varying dosages. Maximum serum concentrations of 0.126 and 0.256 mg/L after a 60 mg and 120 mg dose, respectively, have been reported [222]. Saarialho-Kere et al. [197] reported 0.105 mg/L serum levels 1.5 h after a 100 mg oral dose. One h after a 60 mg dose, serum levels were measured at 0.11 mg/L [25,66]. Within 1 h of a 65 mg intramuscular dose, peak plasma concentrations were measured at a mean of 0.264 mg/L [66].

Approximately 10% of the dose is *O*-demethylated by cytochrome P450 2D6 (CYP2D6) to form morphine. Seven percent of Caucasians and 50% of Chinese subjects have nominally functional polymorphisms of CYP2D6 and are poor metabolizers of codeine [185,217]. Formation of morphine contributes to the analgesic effects of codeine and polymorphisms of CYP2D6 have been attributed to some of the interindividual variation in human response to codeine [26]. *N*-demethylation to norcodeine and glucuronidation to form both codeine glucuronide and morphine-6-glucuronide (M6G) accounts for other metabolites. Morphine predominates in the early phase of excretion, but over 20–40 h morphine conjugates tend to predominate.

Overdose with codeine may be lethal at 0.5–1.0 g doses. Blood concentrations in two individuals arrested for impaired driving were 2.6–7.0 mg/L [12]. Classic presentation of overdose included unconsciousness with pinpoint pupils (miosis) and respiratory depression [60]. Postmortem blood concentrations related to codeine overdose have been reported from 1.4 to 370 mg/L. Symptoms of overdose are reported to respond well to administration of naloxone [95].

## B. Reported Effects on Performance

### 1. Summary of Studies

A variety of studies have looked at various aspects of codeine's effects on performance. The evaluation of effects has been accomplished through the use of a wide variety of performance tests. Readers are referred to Baselt [12] for a concise description of many of these tests. Table 3 summarizes the study designs, tested endpoints, and outcomes of controlled dosage studies. These studies evaluated a broad range of dosages, both chronic and acute, in both non-users and individuals with prior usage history. **Table 4** summarizes a number of studies evaluating the prevalence of drug use in populations involved with driving or driving accidents. These studies also evaluated the relative risks of codeine and opioid use in accidents.

Bradley and Nicholson [22] administered 30, 60, and 90 mg single doses to six healthy females. Subjects were practiced on all tests to steady state performance. Tests included visuo-motor coordination (VMC), dynamic visual acuity (DVA), complex reaction time (CRT), digit symbol substitution test (DSST), and critical flicker fusion (CFF). Triprolidine HCl was used as a positive control. Findings indicated that central effects from codeine dosages were limited to neuromuscular activity in a dose dependent fashion. The 60 and 90 mg doses significantly altered VMC. Codeine did not modulate saccadic and smooth pursuit eye movements, as do other morphine-like compounds.

Evans and Witt [63] examined the effects of a 32 mg dose of codeine on DSST in 16 healthy male volunteers at varying altitudes. Codeine impaired performance on DSST at 2,000 ft, but performance returned to baseline (actually improved relative to controls) at 15,000 ft. The main indication is that a large number of factors affect impairment by codeine.

Heishman et al. [97], evaluated the accuracy of drug recognition expert (DRE) assessment and the ability of various criteria to indicate intoxication by various drugs. Subjects with a prior use history were administered 0, 60, or 120 mg codeine. The results indicated that certain subsets of the evaluated criteria could, to a limited extent, predict acute administration of codeine. Specifically, evaluation of decreased sum of pupillary diameter and decreased rebound dilation of pupils could identify the presence of codeine with moderate efficiency.

Jonasson et al. [110] evaluated 4896 drug screened, suspected driving under the influence (DUID) cases in Sweden from 1992–1997. They found that 7.9% of the cases involved codeine.

Leville et al. [135] examined the relative risk of older drivers (over 65 years of age) on prescription medications for injury in motor vehicles. Two hundred thirty-four cases were investigated with 447 matched controls. The relative risk was determined to be 1.8 with codeine being the most commonly prescribed opioid.

Linnoila and Hakkinen [137] evaluated the effects of codeine alone and in combination with alcohol on performance in a driving simulator. Seventy professional drivers from the Finnish Army were administered 50 mg codeine or 50 mg codeine and 0.5 gm/kg alcohol in a double blind design. They concluded that codeine alone or in combination with alcohol increased risks for collision in both emergency and monotonous driving situations.

Saarialho-Kere et al. [196] examined the effects of a 100 mg dose of codeine alone or in combination with a 0.25 mg/kg dose of diazepam on ten healthy non-users.

**Table 4.** Epidemiological studies examining populations with codeine or morphine present involved in accidents or driving under the influence of drugs

Study Group	Result	Ref.
1446 apprehended drivers 445 with drug tests	26 of 445 found to have morphine present; 15 of 445 with codeine present	[19]
4896 driving under the influence of drug cases	388 had the presence of codeine (mean 0.04 µg/g blood)	[110]
234 injured elderly drivers 447 matched controls	1.8 relative risk for auto accident (55% of use was codeine)	[135]
214 hair analyses of driving license applicants	14 morphine/6-AM positive greater than 0.1 ng/mg hair	[151]
137 driving under the influence of drug cases	15% with opiates present (2 with codeine; 3 with morphine)	[176]
854 auto injury victims	5% demonstrated morphine present and 3.8% demonstrated codeine	[207]
4860 hair analyses of driver license applicants	4.8–6.7 morphine positives per year from 1996–1998	[213]
2962 hair analyses of driver license applicants	12–46% morphine positives (0.54–1.81 ng/mg hair) per year from 1988–1995	[212]

Tests included body sway, DSST, CFF, Maddox-Wing (MW), and gaze nystagmus. Codeine did not have a significant effect on any of these end-points. Subjectively, participants rated themselves as mentally slowed by the codeine dose. Codeine also appeared to reduce the absorption of diazepam.

Walker and Zacny [222] evaluated the psychomotor, subjective, and physiological effects of 0, 60, and 120 mg codeine on twelve healthy volunteers. Tests included the Addiction Research Center Inventory (ARCI) subjective effect questionnaire, a drug effect/liking (DEL) questionnaire, MW, DSST, auditory reaction test, logical reasoning, and short-term and long-term memory tests. Physiological end points included heart rate, blood pressure, arterial oxygen saturation, respiration rate, and miosis. Plasma drug levels were also measured. Peak plasma concentration means were 0.126 mg/L for the 60 mg dose and 0.256 mg/L for the 120 mg dose within 4 h of dosing. Though codeine increased self-reported “feels drug effect”, no other significant effects were measured for codeine.

## II. HYDROCODONE/HYDROMORPHONE

Hydrocodone, dihydrocodeinone, is a semi-synthetic narcotic prepared from codeine that is more toxic than codeine. Hydrocodone is available in syrups and tablets with recommended dosages for adults of 5–10 mg three to four times a day and for children 0.6 mg/kg body weight, divided into three or four doses. An effective antitussive agent, hydrocodone also produces a number of opioid effects such as central nervous system depression, miosis, and an addiction liability. It has been suggested that most of the opioid effects of hydrocodone actually occur from the hydromorphone formed during metabolism.

Hydromorphone, dihydromorphinone, is a semi-synthetic narcotic and µ-agonist opioid. Hydromorphone,

used therapeutically since 1926, is available in tablets of 2, 4, or 8 mg; in syrups of 1 and 5 mg/5 mL; in solutions of 1, 2, 4, or 10 mg/mL for IV, IM, subcutaneous or intrathecal administration; and also in 3 mg rectal suppositories. A controlled-release formula is available in Canada but not in the United States. Hydromorphone is used in post-operative pain management and in the treatment of some cancer pain. The medical use of hydromorphone increased by 19% during the time period of 1990 to 1996. During the same time period, the reports of abuse decreased by 15% [112].

### A. Pharmacology/Pharmacokinetics

During metabolism, hydrocodone is *O*-demethylated to hydromorphone, *N*-demethylated to form norhydrocodone, and C6-keto reduced to form approximately equal amounts of 6α- and 6β- hydrocol [37,38]. CYP2D6 is involved in the metabolism of hydrocodone to hydromorphone. The maximum concentration of hydromorphone seen after a dose of hydrocodone varies (greater than five-fold) between individuals in correlation to their CYP2D6 function. Poor metabolizers excreted significantly more of the unchanged hydrocodone in their urine. Peak plasma concentrations of hydromorphone occurred 1–2 h after a dose of hydrocodone. This potential increase in hydrocodone concentration does not seem to cause a marked difference in the pharmacological effects of a dose of hydrocodone [118,170]. Cone et al. [38] found 14% of the total urinary recovery of a 15 mg dose was hydromorphone, 20% was the *N*-demethylated metabolite norhydrocodone, and 14% was the product of C6-keto reduction.

Oral hydromorphone is five to seven times more potent than morphine, i.e., a 10 mg dose of morphine is equianalgesic to a 1.5–2 mg dose of hydromorphone. This ratio is lowered in those who are opioid tolerant to 3:1 to

5:1. When administered intravenously, hydromorphone is 8.5 times more potent in its analgesic efficacy than morphine and is 60 times more potent than meperidine when administered epidurally.

Hydromorphone by intravenous administration has a rapid onset of effects within 5 min, a short time to peak effects, within 10–20 min, and a relatively short duration of action of between 3–4 h. Dizziness, flushing sensation, sedation, mental confusion, anxiety, fear, dysphoria, nausea, and vomiting are adverse effects of hydromorphone. A log linear dose-effect relationship for analgesia and respiratory depression has been seen across the dose range of 0.5–4 mg in both postoperative patients and normal volunteers [24,35,144]. In patients receiving large doses of systemically administered hydromorphone for pain treatment, neuroexcitatory side effects such as allodynia, myoclonic jerks, and seizures can occur, caused by the hydromorphone 3-glucuronide (H3G) metabolite and may warrant switching the patient to a structurally dissimilar opioid (e.g., methadone or fentanyl). The onset of effects is delayed to 30 to 180 min after non-intravenous administration of hydromorphone. Ritschel et al. [190] found that it took 60 min for 95% of the hydromorphone in a tablet to be released, and 8 h for 60% of the hydromorphone in a cocoa butter suppository to be released. Average terminal elimination half-lives for the various administration routes are 2.4–3 h for intravenous administration, 4.10 h for oral administration, and 3.80 for rectal administration [35,190,219].

Coda et al. [35] found peak plasma concentrations of 0.00803, 0.01411, and 0.02186 mg/L after intravenous administration of 10, 20, and 40 µg/kg doses, respectively. Mean peak plasma concentrations of 0.022 mg/L after oral administration of 4 mg hydromorphone occurred at 1 h [219]. Cancer patients given an average daily dose of 48 mg (range 6–216 mg) of controlled-release and immediate-release hydromorphone showed no significant difference in the steady-state hydromorphone and H3G concentrations. After administration of the controlled-release product,  $C_{max}$  of hydrocodone and H3G were 0.01776 mg/L and 0.40169 mg/L, respectively. Administration of immediate-release drug resulted in  $C_{max}$  of 0.0197 mg/L hydrocodone and 0.36774 mg/L H3G. The pharmacokinetic profiles of immediate-release and controlled-release hydromorphone showed no significant differences over this dosage range [92]. Babul et al. [7] again examined the pharmacokinetic profile of controlled release hydromorphone and found similar profiles when comparing children and adults being treated for pain. The peak concentration of hydromorphone occurs significantly later with controlled-release dosing (12 h compared to 0.8 h for immediate-release), but maintains at 50% of peak concen-

tration for significantly longer (31 h compared to 1.6 h). Similarly, controlled-release hydromorphone produced analgesic effects that peak later and last longer [3].

An effective plasma concentration of 0.004 mg/L was suggested by Reidenberg et al. [188] after examining chronic pain patients. Inturrisi et al. [108] reported a concentration of 0.020 mg/L for half-maximum analgesia in cancer patients. A wide range of effective concentrations was seen in both studies.

Hydromorphone undergoes first-pass elimination following oral administration [190]. Primarily metabolized to H3G, the mean steady-state molar ratio of H3G to hydromorphone was 27:1 in adult cancer patients [92]. Two minor metabolites of hydromorphone, dihydromorphine, and dihydroisomorphine have demonstrated pharmacological activity, but their contribution may be minimal due to the small amount formed. Hydromorphone is primarily excreted in the urine as a glucuronide conjugate (35%) with minor amounts of dihydromorphine and dihydroisomorphine conjugate (2%) and unchanged drug (6%) being found [38,40]. The majority of a dose is excreted in the first 24 h with the free and conjugated drug reaching undetectable levels after 8 and 48 h, respectively [40].

Hydrocodone and hydromorphone have been analyzed in alternate specimen matrices. Moore et al. [153] reported hydrocodone in meconium from two cases. Codeine, morphine, and hydromorphone were also present in one case and morphine in the other. By doing the analysis both with and without hydrolysis, it was shown that hydrocodone is significantly conjugated to glucuronide in meconium. Hydrocodone, at a concentration of 0.62 ng/mg, was found in 1 out of 46 postmortem toenail samples [62]. The half-life of hydromorphone in saliva was found to be 2.12 h (0.93 SD). Initially after IV administration, saliva hydromorphone concentrations are lower than the plasma concentrations. The saliva concentration peaks and then drops parallel to the hydromorphone plasma levels. Therefore, the saliva/plasma ratio varies during absorption, distribution, and elimination. The ratio reached a maximum (approximately 2.3:1) at the time when complete distribution of hydromorphone had occurred (approximately 40 min) and then remained constant (approximately 1:1) during the elimination phase [190].

## B. Reported Effects on Performance

### 1. Summary of Clinical Studies

McCaul et al. [148] gave five male former opioid users 0, 2, 4, or 6 mg of hydromorphone by intravenous injection. A number of physiological parameters were monitored, pupil size was photographed, and subjective

reports were administered every 15 min for 2 h after dosing. A dose-related constriction of the pupils was observed with a mean pupil diameter of 6.3 mm prior to dosing and decreasing by 2.2 and 3.7 mm following the 2 mg dose and 6 mg dose, respectively. Respiration rate decreased during the 2 h post injection. Dose-related increases in all measures followed 2 and 4 mg doses of hydromorphone. No further increase was seen after the 6 mg dose.

Preston et al. [182,183,184] administered 0–3 mg/70 kg hydromorphone to six, five, and seven male subjects, respectively, in three drug discrimination studies. In addition to the discrimination measures, the test battery included a VAS, pharmacological class questionnaire, adjective rating scale and shortened ACRI, physiological measures including pupillary diameter, and DSST as a measure of psychomotor performance. In all three studies, hydromorphone produced some significant scores on the VAS and on a measure of euphoria. Pupil diameter decreased by more than 2 mm after the 3 mg dose. Hydromorphone dosages did not significantly impair performance on the DSST.

Oliveto et al. [164] administered 1–6 mg/kg hydromorphone to seven healthy male and female subjects in a drug discrimination study. In addition to the discrimination measures, the test battery included the ARCI, an adjective rating scale, a VAS, and DSST as a psychomotor measure. Evaluations took place 120 and 150 min after dosing. Hydromorphone did not produce any significant changes in the ARCI or VAS scores, or the performance on the DSST.

Pickworth et al. [174] administered a single oral dose of 1 or 3 mg of hydromorphone to eight male former drug abusers and evaluated their performance on a battery of tests for 5 h after dosing. The test battery included a self-rating of sedation, DSST, a visual search task, circular lights, and arithmetic and card sorting tests. Sedation increased with the high dose and both doses impaired the subject performance on the visual search evaluation.

Walker and Zacny [223] found an orderly dose-response during an increasing dose cumulative-dosing regimen where subjects were given 0.33, 0.65, and 1.3 mg/70 kg IV of hydromorphone with 1 h between each dose. Psychomotor and cognitive performances were measured using MW, an eye-hand coordination test, an auditory-reaction test, a logical-reasoning test, and DSST. Five physiological measures were also assessed. Hydromorphone was as likely to produce drug liking as drug disliking. The unpleasant subjective effects continued 4 h after the last injection. Hydromorphone significantly increased subjective sedation and caused dose-proportional miosis. The psychomotor performance of the subjects was more

impaired in this study than in previous single dosing studies. These results indicate the potential for cumulative effects from multiple doses. Hydromorphone caused dose-proportional impairment on the MW, DSST, and tracking tasks.

Hill and Zacny [100] looked at effects of single doses of hydromorphone from 0.33–1.3 mg/70 kg IV. The study looked at subjective measures, psychomotor/cognitive performance, and physiological effects. Patients reported both drug liking and ratings of “feel bad”. Dizziness, sedation, nausea, and vomiting occurred. Pupil diameter and respiration rates decreased proportionally with increased drug dosage. Hydromorphone, at the highest dose tested, impaired performance on DSST, but did not affect reaction time, eye-hand coordination, logical reasoning, or memory processes. The degree of impairment was mild compared to impairment with clinical doses of benzodiazepines and other sedative drugs. Morphine at 10 mg also used in this study showed no psychomotor impairment.

## 2. Summary of Epidemiological Studies

Farrell and Cada [64] reported toxicology statistics for 1194 urine specimens submitted by Drug Recognition Experts collected over a two year period from subjects suspected of DUID. Narcotic analgesics were identified in 100 specimens (8.4%). Hydrocodone was identified in 25 of these specimens. It was the only opioid identified in 19 of the 25 specimens.

DiGregorio et al. [47] tabulated demographic information and drug concentrations from 686 DUID cases with 619 cases deemed to be prosecutable. Hydrocodone was identified in one case; the concentration in the blood was 0.225 mg/L.

## III. METHADONE

Methadone was developed during World War II as a substitute for morphine and heroin. It became available for clinical use in the United States in 1947. Twenty years before methadone maintenance began, methadone was first used by the Public Health Service facility in Lexington, Kentucky to gradually withdraw opioid addicts. In 1965 methadone was formally introduced as a substitution treatment for opioid dependence. Methadone is now the most widely used pharmacological agent in the treatment of opioid dependence with over 100,000 patients enrolled in methadone maintenance programs.

Methadone maintenance programs still remain controversial thirty years later. Replacing heroin with methadone has not cured all of the problems associated with addiction. Overdose deaths, the use of illicit drugs, infections, and crime are still present. Methadone maintenance

programs have significantly reduced the number of deaths, reduced the occurrence of infection with HIV, and have decreased the amount of criminal behavior in the community.

### A. Pharmacology/Pharmacokinetics

Methadone, a long-acting  $\mu$ -agonist indicated for the relief of moderate to severe pain, is approximately equipotent to morphine as an analgesic when administered parenterally. Commercially available under the trade name Dolophine, methadone is supplied as the hydrochloride salt of the racemic mixture.

(R,S)-methadone = rac-methadone = *d,l*-methadone  
= racemic methadone; 50:50 mixture

(R)-methadone = *l*-methadone = levomethadone

(S)-methadone = *d*-methadone

The pharmacological activity is almost entirely due to (R)-methadone. With a ten-fold higher affinity at  $\mu$  and  $\delta$  opioid receptors, (R)-methadone has been shown to have 50 times the analgesic activity of (S)-methadone in human and animal studies. (R)-methadone prevents the occurrence of opioid withdrawal symptoms while (S)-methadone is ineffective. For oral usage, methadone is available in tablets of 5 or 10 mg, diskettes of 40 mg or as a syrup of 1, 2, or 10 mg/mL. A 10 mg/mL solution is also available for parenteral injection. The maximal direct opioid effects occur approximately 3 h after methadone ingestion causing sedation, altered perception and response to pain, and general central nervous system depression. The subjective effects of low psychomotor speed, alertness, running nose, yawning, and anxiety were all found to have a significant association to plasma concentration in methadone maintenance patients studied over a 24 h period [101]. Although 50 mg or less has proven fatal in non-tolerant adults, as much as 180 mg/day may be used in methadone maintenance programs and in rare incidences up to 780 mg/day have been required to prevent illicit opioid use in some patients. Most deaths that are related to methadone occur during the first few weeks of methadone maintenance treatment when fatal respiratory depression is a risk.

After oral administration, methadone is rapidly absorbed from the gastrointestinal tract, and is detectable in the blood within 30 min. Oral bioavailability of total methadone varies from 41–99%. Bioavailability after oral administration showed no difference between enantiomers indicating no stereoselectivity in the passive diffusion process. (R)-methadone bioavailability ranged from 66.8–100% and (S)-methadone ranged from 65.5–100% [131].

The volume of distribution of methadone is large with average values ranging from 4–6.7 L/kg. With a single dose, (R)-methadone has a lower protein binding and therefore has a larger volume of distribution than (S)-methadone. In opioid users receiving long-term oral methadone, the mean distribution half-life has been reported to be 5.8 h.

Values for terminal half-life indicate differences between the two enantiomers and between healthy subjects and opioid addicts. (R)-methadone has a longer terminal half-life, average 37 h (range 30–59) compared to 28 h (range 18–41) for (S)-methadone [129,131,160]. The racemate terminal half-life ranges from 13–60 h. Healthy subjects, who had never taken methadone, had a shorter terminal half-life than opioid patients at the beginning of treatment who in turn had a shorter terminal half-life than opioid patients at steady-state [104,231,234].

Mean oral clearance in healthy subjects and opioid patients showed the same trend regarding the difference between enantiomers in healthy subjects and opioid patients. Kristensen [131] found clearance rates of 158 mL/min and 129 mL/min for (R)- and (S)-methadone respectively and 96 mL/min for the racemate. Wolff [234] compared healthy subjects with opioid users and found mean oral clearance rates of 115 mL/min and 53 mL/min, respectively.

Although the pharmacokinetics of methadone are stereoselective, a highly significant relationship between plasma AUC and dose exists for both (R)-methadone and (S)-methadone. This indicated that the pharmacokinetics of each enantiomer were linear after administration of the racemate over a wide dosage range, 7.5–130 mg/day, in separate individuals [70].

Following treatment with the same methadone dose, large inter-individual variation of methadone plasma concentrations have been documented. This variation ranged between seven and seventeen fold [54,55]. A detectable increase in the plasma concentration occurred within 15 to 30 minutes peaking between 1–4 h after oral dosing [45,231]. Peak plasma concentrations after 15 mg, 100–120 mg, and chronic administration of 100–200 mg doses were 0.075 mg/L, 0.86 mg/L, and 0.83 mg/L, respectively. The range of peak plasma concentrations seen after high chronic dosing was 0.57–1.06 mg/L [106]. The peak plasma concentration after an intravenous dose of 10 mg was 0.50 mg/L [104]. The use of methadone intravenously resulted in a higher concentration to dose ratio of (R)-methadone (23% increase) due to the loss of metabolism in the gut wall and loss of the liver first-pass effect [65]. Large interindividual variability in the (R)/(S) plasma ratio of methadone occurred. Eap et al. [55] found a range of 0.63–2.4 in plasma samples of 22 addict patients under

racemic methadone maintenance treatment and a range of 0.55–2.55 (mean 1.14; SD = 0.37) with a larger population of 211.

Trough methadone concentrations, those found just prior to the next methadone dose have also been determined. Eap et al. [54] found for 50 methadone maintenance patients receiving 30–230 mg/day (mean 95±44) trough plasma concentrations of (R)-methadone to range from 0.060 to 0.583 with a mean 0.152±0.091 mg/L, (S)-methadone to range from 0.033 to 0.511 with a mean of 0.144±0.092 mg/L, and (R,S)-methadone trough plasma concentrations to range from 0.097 to 1.094 with a mean of 0.296±0.176 mg/L. Eap [55] measured the trough plasma concentration of (R)-, (S)-, and (R,S)-methadone to examine the correlation between plasma concentration and therapeutic response (defined as the absence of illicit opioid use). A large interindividual variability in (R)-methadone concentration-to-dose-to-weight ratios (mean, SD, median, range: 112, 54, 100, 19–316 ng × kg/mL × mg) was found. This translates into a theoretical dose of racemic methadone ranging from as little as 55 mg/day to as much as 921 mg/day to produce a plasma (R)-methadone concentration of 0.250 mg/L in a 70-kg patient. With regard to consumption of illicit opioids, a therapeutic response was associated with (R)- at 0.250 mg/L and (R,S)-methadone at 0.400 mg/L but not with (S)-methadone concentrations. These results both support the past guideline of 0.400 mg/L that has been used in therapeutic drug monitoring of methadone patients and indicate that specific monitoring of (R)-methadone may be necessary in cases of continued intake of illicit opioids.

Fifteen patients with pain caused by cancer were administered methadone by continuous infusion for a period of 180–270 min. An increase in pain relief and/or sedation was seen with increasing plasma methadone concentrations. The mean estimated values for 50% of maximum effect for both pain relief and sedation were essentially the same for the group (0.359 mg/L and 0.336 mg/L) but the range for each varied ten to twenty fold between patients. Throughout the study no development of tolerance to the pharmacodynamic effects of methadone was seen [105].

Differences in responses between “holders” (no withdrawal symptoms between dosing) and “non-holders” (withdrawal symptoms) are due to variations in individual pharmacokinetics. Specifically, small changes in plasma concentrations translate into large changes in effect. Clinically important withdrawal is a consequence of rapidly declining methadone concentration. Changes in mood are exaggerated in those patients experiencing significant withdrawal. In comparison to controls, methadone pa-

tients showed increased anger, depression, tension, confusion, and fatigue, as well as decreased vigor [52,53]. Once-daily dosing may not work for up to one-third of the population. These patients may require a split dose or an alternative to methadone if they are to be successful in their addiction treatment program.

The data on blood levels in deaths attributed to methadone toxicity show no significant difference from levels in methadone maintenance subjects or those having died where methadone is present but was not the cause of death. Worm et al. [237] found blood methadone concentrations averaged 0.28 mg/L (range 0.06–3.1) in 59 victims of fatal methadone overdose. Sixty-two methadone maintenance subjects used as controls had blood methadone concentrations of 0.11 mg/L (range 0.03–0.56). Thirty-eight cases occurred during 1997 and 1998 at the Office of the San Francisco Medical Examiner in which methadone was detected. Seventeen of these cases were deemed to have been caused by methadone toxicity. The mean blood concentration for all 38 patients was 0.957 mg/L, (SD = 0.681, SE = 0.14). The mean blood concentration of EDDP was 0.253 mg/L, (SD = 0.529 mg/L, SE = 0.089). The mean ratio of methadone to EDDP was 13.6:1 [119]. Milroy and Forrest [150] examined 111 death cases in which 55 cases had methadone poisoning given as the sole cause of death. Five victims were under the age of 14 and fifty victims were adults with a mean methadone concentration of 0.584 mg/L (median 0.435; range 0.084–2.700). In 56 cases, death was ascribed to a combination of methadone and other drugs. Mean methadone concentration in these cases was 0.576 mg/L (median 0.294; range 0.049–2.440). Multiple site sampling in 26 cases revealed that there could be a 100% discrepancy between methadone concentrations from different sites. EDDP concentrations have been suggested as a method to distinguish between acute and chronic use and again chiral analysis has the potential to offer the most beneficial information.

Methadone is primarily eliminated from the body by metabolism in the liver. A total of nine metabolites of methadone have been identified in human urine. Methadone is metabolized to two minor pharmacologically active metabolites: methadol and normethadol. The primary metabolic pathway for methadone is by mono- and di-*N*-demethylation, followed by spontaneous cyclization to form 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) and 2-ethyl-5-methyl-3,3-diphenylpyrrolidine (EMDP). The process of *N*-demethylation has been shown to not be markedly stereoselective. Methadone, EDDP, and EDMP also undergo hydroxylation in the para-position of one of the phenyl rings and glucuronide conjugation.

Methadone is metabolized extensively by the cytochrome P450 enzymes, primarily via CYP3A4, with possible involvement of CYP2C9 and CYP2C19. There are mixed reports in the literature regarding the involvement of isoenzymes CYP1A2 and CYP2D6, with CYP2D6 preferentially metabolizing (R)-methadone. Following a single oral dose of methadone, unchanged methadone and EDDP account for up to 50% of the dose. Other identified metabolites contribute very little, quantitatively. Methadone may account for 5–50% of the dose in 24 h urine specimens of methadone maintenance subjects with EDDP accounting for 3–25% of the dose. Since methadone is a weak base, urinary pH has a marked effect on its excretion into urine. Acidifying the urine resulted in an increase in the amount of unchanged methadone excreted, leading to increased drug clearance. Nilsson et al. [162] found excretion percentages of 22% of the prescribed dose in 24 h for acidic conditions compared to only 5% under alkaline conditions. Less effect of urine pH on EDDP excretion was observed. Variations in urine drug concentrations also are effected by urine volume, dose, and rate of metabolism. Patients excrete significantly more (R)-methadone and (S)-EDDP than the corresponding enantiomers. Lesser amounts of EDDP are found in the feces, 6–18%, with methadone found at less than 1% of the dose.

Other drugs that compete for the same binding sites in the plasma, or that are metabolized by the same enzymes in the liver, can modify the action of methadone. Sertraline inhibited methadone metabolism in the first six weeks of treatment causing an increase in plasma methadone levels. Plasma levels returned to baseline by week twelve [93]. The antituberculosis drug Rifampin lowered methadone plasma levels, but Rifabutin did not affect methadone kinetics. Within the group of anti-epileptic drugs, phenytoin lowered blood levels of methadone, and phenobarbital and carbamazepine increased methadone metabolism. Plasma levels of methadone increased by 20–100% in the presence of the benzodiazepine fluvoxamine increasing the risk of fatal respiratory depression. Buprenorphine at doses of 1 and 2 mg is a morphine agonist. Pure morphine agonists increased the risk of respiratory depression while partial agonists increased the likelihood of withdrawal symptoms [200]. Concomitant use of amitriptyline lowered the plasma concentration of methadone by increasing the plasma concentration of alpha 1-acid glycoprotein, the main binding protein of methadone in the blood. Only a few of the many potential interactions have been studied. A list of medications that potentially could influence methadone metabolism due to an effect on CYP3A4 can be found at the URL “[www.urmc.rochester.edu/urmc/AAPCC/tables.html](http://www.urmc.rochester.edu/urmc/AAPCC/tables.html)”. Drugs of abuse also have been shown to affect methadone blood levels. Accelerated metabolism

of methadone occurred when taken by cocaine users [215]. Methadone and alcohol compete for CYP450 enzymes, thereby slowing metabolism in acute intake [43] and potentially increasing metabolism in alcoholics that become abstinent [130].

Methadone elimination is significantly more rapid for pregnant patients (half-life 19 h) compared to non-pregnant patients (half-life 30 h). Pregnancy may also decrease the fraction of methadone absorbed, thus impacting the apparent clearance and volume of distribution. Differences in hormone concentrations during the phases of pregnancy could significantly alter the absorption of orally administered drugs, such as methadone. Less extensive methadone gastrointestinal absorption may also contribute to lower plasma concentrations during pregnancy [109].

Interindividual variation is too great to correlate urinary excretion concentrations of methadone or EDDP to methadone dose. This relationship does not improve with correcting for creatinine concentration in urine specimens. If a single subject is repeatedly monitored over a period of several days, it may be possible to determine a trend for that individual. However, this requires quantitation of every urine specimen and therefore is not practical [77]. Urine concentrations of methadone in seventeen cases of methadone toxicity were similar between the cases in which death was deemed to have been drug related and those in which it was not. A mean concentration of 5.2 mg/L (SD = 3.6 mg/L) was found in drug related cases and 5.86 mg/L (SD = 6.4 mg/L) in cases where methadone was an incidental finding. The concentration of EDDP also did not differ significantly between the two groups. For drug related deaths, the EDDP concentration was 6.55 mg/L (SD = 5.6 mg/L) compared to 11.8 mg/L (SD = 16.7 mg/L) in cases where methadone was an incidental finding [119].

Methadone has been identified in many alternate matrices. Stolk et al. [208] found a positive relationship between the concentration of methadone in meconium and the methadone dose of the mother. EDDP concentration did not relate to dose. The amount of EDDP in meconium was 9.6 times higher than the concentration of methadone with EDDP only found in eight out of 39 meconium samples from 16 neonates over a period of seven days. ElSohly [61] analyzed 50 pooled meconium samples. All samples screened negative by EMIT-ETS immunoassay. GC-MS analysis showed that four contained methadone (35.2–79.9 ng/g), EDDP (28.5–557.2 ng/g), or both, with no detectable amount of EMDP. The screening false negatives were attributed to the immunoassay being targeted to methadone and not its metabolites.

Nail clippings (0.18–16.33 mg) were collected from 30 adults participating in a methadone maintenance program. Decontamination of the nails was followed by base hydrolysis. The samples were screened for methadone by EIA and confirmed by GC-MS. The mean methadone concentrations in the fingernail clippings determined by EIA and GC-MS were 32.8 and 26.9 ng/mg, respectively [132].

Wilkins et al. [227] found hair concentrations ( $n = 2$ ) ranging from 10.1–21 ng/mg methadone and 0.5–2.6 ng/mg EDDP. Kintz et al. [126], using enzymatic hydrolysis followed by solid-phase extraction and analysis by LC-ion spray-MS, analyzed nine hair specimens from subjects under racemic methadone treatment, and found 2.58–10.22 ng/mg of (R)-methadone, 1.89–9.53 ng/mg of (S)-methadone, 0.42–1.73 ng/mg of (R)-EDDP, and 0.40–2.10 ng/mg (S)-EDDP. The results support the predominance of the (R)-enantiomer of methadone in human hair. Goldberger et al. [83], using GC-MS, analyzed 20 hair samples collected from heroin users enrolled in an outpatient detoxification study and found concentrations of 0–15 ng/mg of methadone and only traces of EDDP. Girod and Staub [80] used GC-MS-positive ion chemical ionization to analyze hair samples from 26 long-term methadone therapy patients. They found no significant correlation between methadone dose and its concentration in hair. They also found no significant correlation between methadone concentration in blood and in hair. Quantitation of EDDP was possible in only approximately 50% of the cases (LOQ 0.2 ng/mg). Methadone concentrations ranged from 0.7–43 ng/mg (0.1–0.6 mg/L in blood) and EDDP in thirteen samples ranged from 0.3–5 ng/mg. No EDDP was found in the blood samples using an LOQ 0.05 mg/L.

Methadone levels in breast milk have also been studied. Two women on high doses of methadone showed minimal transmission of methadone into breast milk regardless of the mother's methadone dose [78]. In a study by Wojnar-Horton et al. [229] twelve women receiving 20–80 mg/day of methadone supplied breast milk samples for analysis. Assuming an average milk intake of 0.15 L/kg per day, and a bioavailability of 100%, the exposure to the infants was calculated to be 17.4 (10.8–24) micrograms/kg per day (2.07–3.51% of the maternal dose). No adverse effects were attributable to methadone in the milk. Another group of eight women on doses of 25–180 mg/day of methadone were found to have breast milk levels of methadone that ranged from 27–260 ng/mL, with a mean methadone level of 95 ng/mL. The mean daily methadone ingestion, based on a newborn intake of 475 mL/day of breast milk, was 0.05 mg/day [147].

Saliva concentrations of methadone have been evaluated. Methadone with a pKa of 8.3 is largely ionized at the unstimulated salivary pH of 5.6–7 and tends to accumu-

late in the saliva. A slight change in saliva pH will affect the diffusion of methadone. An inverse relationship exists between saliva pH and methadone concentration. The salivary concentration of EDDP was not influenced by salivary pH [17]. The reports of saliva/plasma ratio of methadone vary in the literature with reported values of 0.51–10 [17,59,116,142,230]. Total methadone determination correlates poorly between saliva and serum. Orтели et al. [169] again found no correlation between serum and saliva concentrations but did establish a good correlation ( $r^2 = 0.91$ ) between the (R)/(S) ratio of the two matrices. One hundred clinical samples from heroin addicts that had reached steady state in their methadone treatment were analyzed. Preferential binding of (S)-methadone to blood protein produced a higher (R)/(S) ratio in saliva, between 1 and 9, when compared to the (R)/(S) ratio in blood that ranged between 0.5 and 3. Bermejo et al. [17] cautions that the method of collection can greatly influence the concentration of drug in the saliva sample. Collection with Salivette resulted in 30–40% lower concentrations of methadone and EDDP when compared to the direct spitting method of collection.

Sweat patches were applied to 20 subjects that received 80–100 mg of racemic methadone. The sweat patches remained in place for 72 h. Subsequent enantioselective separation and analysis of methadone was done by liquid chromatography/ion spray-mass spectrometry. (R)-methadone was found in concentrations ranging from 26–1118 ng/patch and (S)-methadone was found in concentrations ranging from 28–1114 ng/patch. The (R)/(S) ratio ranged from 0.72–2.66 with it greater than 1.00 in fifteen samples. No correlation was found between the dose of methadone and the concentration of methadone in the sweat patch [127].

## B. Reported Effects on Performance

### 1. Summary of Clinical Studies

**Table 5** provides a summary of methadone controlled administration studies while **Table 6** provides a summary of population studies.

Gordon et al. [87] examined Wechsler Adult Intelligence Scale (WAIS) scores of 155 methadone maintenance patients on doses ranging from 70–100 mg per day and found no departure from the expected normal population IQ distribution. Gordon and Lipset [86] administered this same test to thirty of these same subjects in a follow-up study and again found normal intellectual functioning.

Gordon [88] compared the performance of methadone patients and control groups on three reaction time tests. The control groups consisted of non-drug using subjects and detoxified heroin users. Simple reaction time, multiple discrimination/multiple response reaction

**Table 5.** Overview of controlled administration studies of methadone with psychomotor and cognitive effects

Dose	Study group <sup>a</sup>	End point measured <sup>b</sup>	Effects <sup>a,b</sup>	Ref.
70–100 mg	155 MM	WAIS	No departure from normal population IQ	[87]
Maintenance	MM/CTR	SRT, CRT	MM reaction times faster than controls	[88]
Maintenance	MM/CTR	SRT	No effect of methadone on reaction time	[85]
35–85 mg	10 MM/5 CTR, 10 abstinent	PHYS, EEG, CMI, MAACL, DSST, COT, HWT, etc.	EEG difference related to dose; no reaction time deficit; significant impairment on attention, perception and learning tasks	[90]
80–120 mg	MM/CTR	DSST	No impairment to attentional function	[4]
50, 80 mg	38 MM	WAIS	No performance difference between the dosages	[139]
20–70 mg	12 MM/12 CTR	SRT, vigilance	No reaction time deficit in MM; dose-related slowing of reaction time in CTR; CTR with impairment to vigilance, MM improvement	[195]
20–120 mg	30 MM	Distance and time, SRT, CRT, memory, attention	Only distance perception impairment reached significance	[122]
Maintenance	MM/CTR	Visual function, tracking, psychomotor, perceptual, instrumented car	Impairment to rate of information processing in MM	[158]
5 or 10 mg	Non-addicts	Eye movements	Driver will obtain less information and suffer a loss of visual acuity	[194]
Maintenance	MM/CTR	Sustained attention	No difference between groups	[5]
60–110 mg	15 MM/16 CTR	Information processing, divided attention and tracking	MM showed a slower rate of information processing from immediate to short-term memory	[192]
Maintenance	MM/CTR	3 tracking tasks SRT	No significant performance differences in groups	[157]
10–180 mg	34 MM	SRT, verbal and visual memory, attention, and concentration	Methadone plasma levels: 0.09–1.32 mg/L; 22/34 achieved score necessary for driving test	[193]
17.5–60 mg	13 MM/13 CTR	Short term memory, tracking, decision and reaction time, perception, attention, personality	6 MM = control performance, all others poorer; significant decrement in tracking, reactive stress; psychopathological shortcomings large factor; general opinion: unfit to drive	[206]
100 mg (average)	34 MM	Preliminary evaluation	No significant loss in performance; 70% had psychiatric disorders;	[76]
15–150 mg, diazepam 15 mg, ethanol 0.064%	MM (3 groups) CTR (2 groups)	CTT, VST	No effect of the acute or increased dose of methadone; methadone impairment less than ethanol or diazepam; poorer performance of MM attributed to other factors	[28]
29/34 ≤ 60 mg	34 MM	Concentration, attention, reaction, memory, coordination	Methadone only — no impairment; 2/3 had positive urine test for multiple drug use; mixed drug use and personality disorders is of greater importance	[96]
Maintenance	28 MM/28 CTR	Traffic relevant tests	6 out of 28 had sufficient driving skills; majority showed reduction of psychomotor skills	[48]
Maintenance	30 MM/30 CTR	Information processing, memory, attention, problem solving	Cognitive impairment in MM (almost 50% severely impaired); high rates of psychiatric morbidity, increased exposure to overdose and history of alcohol dependence	[44]
Maintenance	54 MM/54 CTR	Attention, perception, reaction time, tracking, visual structuring	54% had no results out of the normal range; felt observed variances better explained by sociodemographic factors	[205]

<sup>a</sup> MM: Methadone maintenance subject; CTR: Control subject.

<sup>b</sup> WAIS: Weschler Adult Intelligence Scale; SRT: Simple reaction time; CRT: Complex reaction time; PHYS: Physiological testing (varied combination of heart rate, blood pressure, skin temperature, etc.); EEG: Electroencephalograph; CMI: Cornell Medical Index; MAACL: Multiple Affect Adjective Checklist; DSST: Digital symbol substitution test; COT: Cross-Out Test; HWT: Hidden Word Test; CTT: Complex tracking task; VST: Visual search task.

**Table 6.** Epidemiological studies examining populations with methadone present involved in accidents or driving under the influence of drugs

Study Group <sup>a</sup>	Result <sup>a</sup>	Ref.
1562 MM/1059 CTR	Interview and driving records indicate no difference in violation rate	[20]
448 MM/182 CTR	Driving records showed no difference in violations or accident rate	[6]
104 addicts prior to and after MM	MM — Increase in speeding violations; no accident rate difference	[143]
1882 fatal drivers	Toxicology analysis of blood; prevalence rate of methadone: 0.1%	[216]
1194 DRE – DUID cases	Urine toxicology found methadone in 13 specimens (1.1%)	[64]
462 traffic cases (36.6% accidents, 63.4% DUID)	Methadone third most frequent drug in DUID cases; fifth most frequent in accident cases; multiple drug use common in methadone cases	[120]

<sup>a</sup> MM: Methadone maintenance subject; CTR: Control subject; DRE: Drug recognition expert; DUID: Driving under the influence of drug.

time, and multiple discrimination/single response reaction time were all evaluated. The reaction times of the methadone groups were faster than those of both control groups with the non-drug using control group being slowest. The results were attributed to greater motivation, higher level of arousal, and pre-addiction differences.

Gordon and Appel [85] compared the auditory reaction time performance of methadone patients 1 h post dosing and 24 h abstinent from their daily dose. No effect of methadone was observed on patient reaction time; they were either equal to or shorter than those of control subjects.

Gritz et al. [90] determined that methadone intake influenced the gross appearance of the EEG spectra. Furthermore, the level of dosage affected the degree of EEG differences. EEG differences were seen in subjects in an abstinent group for three months. Physiological and psychological measures were also evaluated in the same ten methadone subjects and ten abstinent control subjects. The psychological battery that was used to determine the cognitive ability and emotional state of each subject included the DSST, learning and recall tests, a number of recognition tests, and questionnaires to assess mental health. Respiration and heart rate were lower in the methadone subjects. Methadone subjects showed impaired performance on attention, perception, and learning tasks. No reaction time deficit was observed.

Appel and Gordon [4] used the DSST to assess the performance differences between four subject groups. Two groups were methadone maintenance patients, those with and without jobs, who received 80–120 mg of methadone per day. The other two groups served as controls and were comprised of drug-free former heroin users and drug-free subjects with no history of opioid abuse. Attention functions, as determined by the DSST, were not impaired.

Lombardo et al. [139] assessed the difference in impairment between two dosage groups (50 mg and 80 mg) of methadone maintenance subjects. No significant difference between the two groups was seen on the WAIS.

Rothenberg et al. [195] examined attention capability in twelve methadone maintenance patients, receiving 20–70 mg per day, and twelve control subjects. A vigilance task and a 110 item simple reaction time task were used for this assessment. A monetary reward for performance was offered. The methadone subjects showed significantly shorter simple reaction times and missed significantly fewer responses. When 5 or 10 mg of methadone was given to the control subjects they exhibited a dose-related slowing of reaction time. No change in reaction time after methadone dosing was seen in any methadone subject. For all subject groups, the pre-drug reaction times were shorter with the monetary incentive than without the incentive. The vigilance task showed no pre-drug differences between the groups. After drug administration, the control group showed a decrement in performance while the methadone subjects showed improvement. Methadone patients were able to take up to half again their normal methadone dose without a decrease in performance on these tasks.

Kelley et al. [122] assessed the ability of subjects (methadone maintenance patients) to engage in necessary everyday activities through a battery of tests given 1 h and 24 h post dose. The thirty subjects' methadone dose ranged from 20–120 mg per day. The battery of tests included auditory threshold, distance perception, simple and differential reaction time, time perception, short-term memory, and attention span. The test design was meant to detect any differences in performance that could be associated with an increase or decline in blood methadone concentration. A decrement in distance perception was the only significant result.

Moskowitz and Sharma [157] compared the responses of patients on a methadone program with those of matched drug-free former addicts performing tests of visual function, psychomotor, perceptual, and tracking tasks as well as tests of oculomotor functions. Only a decrement in performance in the rate of information processing by the methadone patients was observed. An instrumented car on a closed course was also used to compare driving performance of methadone patients and drug-free former addicts. No consistent group differences were identified.

Rothenberg et al. [194] looked at the effect on saccadic and smooth pursuit eye movements of 5 or 10 mg of methadone given to non-addict volunteers. In these non-tolerant subjects, methadone delayed the initiation of the saccade, caused an increasing undershoot of the saccade, and reduced the gain of smooth pursuit tracking. The ramifications to driving were that the subject would obtain less information about a target and suffer a loss in visual acuity.

Appel [5] examined sustained attention of methadone patients, drug free ex-addicts, and opioid naïve subjects on a continuous performance task. Overall, no difference was seen between the groups.

Robinson and Moskowitz [192] assessed information processing, divided attention performance and tracking performance of 15 male ex-heroin users in a methadone maintenance program receiving 60–110 mg of methadone daily with that of 16 male ex-heroin users that were drug-free. Both groups performed the test battery twice with 2 h between sessions. The methadone group was given their dose of methadone at the completion of the first session. The methadone maintenance subjects processed information from immediate to short term memory more slowly. This was attributed to long-term methadone intake and not the single dose taken during testing. The methadone subjects showed no performance decrements in visual acuity, tracking performance, visual search rate, reaction times, or peripheral vision in divided attention conditions.

Moskowitz and Robinson [157] examined the performance of methadone patients and ex-heroin users on three different tracking tasks that evaluated compensatory, pursuit, and critical tracking. Again, as in the study above, the testing took place prior to dosing and 2 h post dosing. There were no significant differences in performance across treatment sessions or between groups.

Rosslar et al. [193] examined 34 Austrian probationers undergoing substitution treatment for at least six months with the dosage of methadone ranging from 10–180 mg. The methadone plasma levels correlated well with the administered dosage and ranged between 0.09 and 1.32 mg/L. Subjects were assessed on reaction rate, verbal memory performance, recent visual memory, at-

tention, and concentration. Twenty-two out of thirty-four achieved the average performance necessary to assess them as able to drive in every psychological test.

Staak et al. [206] evaluated 13 methadone patients and 13 matched control subjects. The methadone patients yielded significantly poorer results than the control group when evaluated for short term memory, tracking, decision and reaction behavior, perception, sustained attention, speed estimation, peripheral attention, and reactive loading. Personality questionnaires revealed methadone patients to be more apprehensive, have less self-control, to be less self-reliant, and mentally less healthy. Six patients were singled out as “very good patients”, optimal methadone therapy patients, by the physicians. The differences between their performance and the performance of the control group were insignificant but some differences in personality traits remained.

Gastpar [76] studied 34 methadone patients receiving an average of 100 mg methadone/day. Preliminary evaluation of all subjects did not reveal any significant performance impairment due to methadone. However, the results varied greatly. Twelve had not taken other drugs, ten had consumed cannabinoids and twelve other psychotropic drugs in addition to methadone. The author stresses the need for evaluation of the psychological state of the patient in each case as approximately 70% of the patients revealed psychiatric disorders.

Chesher et al. [28] used three tasks to evaluate performance on skills necessary for driving a motor vehicle. The evaluation included a divided attention task that was composed of a compensatory tracking task (CTT) and a visual search task (VST) conducted simultaneously, a critical tracking task, and a vigilance task. Subjects were dosed with methadone, alcohol (0.064%), diazepam (15 mg), or combination methadone and alcohol, or methadone and diazepam. Three groups of methadone clients were evaluated and divided based on their exposure history. One group consisted of stabilized methadone clients that had been on the same dose of methadone for at least six months with a mean methadone dose of 85 mg (range 40–150 mg). The second group consisted of clients beginning the methadone program with a mean dose of 38 mg (range of 15–60 mg). The third group consisted of clients that were receiving an increase of 10 mg per day in their methadone dose; the mean dose of this group was 67 mg with a range of 40–135 mg. Control groups included ex-opioid users that were currently drug free and non-opioid users. No effect of an acute dose of methadone was seen in any of the experimental groups. Both alcohol and diazepam produced a significant decrement in tested performance by both control groups and the stabilized methadone group. There was no indication of interaction be-

tween the methadone and either the alcohol or the diazepam in the stabilized methadone subjects. The overall scores on the test battery showed a trend for poorer performance by the methadone clients, just reaching significance for the stabilized group. The performance decrement was considerably less than that of subjects dosed with alcohol alone. It was the opinion of the authors that the pharmacological effects of methadone were not the cause of this slightly poorer performance. They suggested that factors including unemployment, life-style, and social and personality disorders could play a contributory role.

Hauri-Bionda et al. [96] studied the effect of a therapeutic methadone dose on traffic-related performance of drivers. Thirty-four subjects, the majority of which were on a low dosage of maintenance methadone (up to 60 mg/day), were evaluated by a psychophysical test battery that consisted of ten individual performance tests. These tests assessed concentration, attention, reaction capability, memory, perception, and sensor-motor coordination. Urine testing of 2/3 of the test subjects revealed evidence of other drug use with cannabis metabolites being most frequently found. Compared to the control group, the methadone group achieved lower results for almost all variables. Performance deficits were most obvious in sustained attention capability, sensor-motor coordination, and reaction capability. Twelve subjects that showed no other drug consumption performed better than the methadone group as a whole, but results still tended to be poorer than the control group. "Methadone only" subjects with no current subjective methadone influence had results that equaled the control group and/or test norms. For subjects that consumed other psychotropic drugs during the subjective methadone phase, a marked impairment to sustained attention and reaction time was observed. This study supported previous research showing that under certain conditions, subjects on long-term methadone maintenance can perform equal to a control group on this psychophysical test battery. Driving ability of the methadone substitution patient does not depend on the methadone therapy itself nor on the amount of methadone taken but on the presence of mixed drug use and the personality of the person.

Dittert et al. [48] looked at the driving ability of patients in a methadone substitution program. Twenty-eight patients were compared to an equal control group. Only six of the methadone patients were deemed to have sufficient driving skills. There was no significant correlation with a patient's age or dose of medication. Methadone substitution did not result in driving inability but the majority of these patients did show reduction in their psychomotor skills.

Darke et al. [44] compared the cognitive performance of 30 methadone maintenance patients to that of 30 non-heroin control subjects. All subjects were (a) interviewed to discover information on drug use history, (b) assessed for psychological distress through the General Health Questionnaire, and (c) completed the WAIS, the Weschler Memory Scale-Revised, the California Verbal Learning Test, the Complex Figure Test, the Controlled Oral Word Association Test, and the Wisconsin Card Sorting Test. This battery of tests was used to determine the subject's ability to process information, pay attention, learn, remember, and problem solve. The methadone subjects were found to have a significantly higher rate of alcohol dependence, heroin overdose, and head injury. As a group, the methadone subjects performed significantly poorer on all of the neuropsychological measures. Information processing, attention, short-term visual memory, delayed visual memory, short-term verbal memory, long-term verbal memory and problem solving all showed decreased performance. Almost half of the methadone subjects in this study had cognitive impairment in the severely impaired range. As expected due to the long-term stability of the patients, no significant correlation between methadone dose and performance was seen among the methadone group. The researchers concluded that while neither heroin nor methadone are neurotoxic, other factors associated with heroin use have implications for cognitive impairment and leads one to suspect an excess of cognitive impairment among methadone maintenance patients. These factors can be divided into three categories: overdose (brain damage due to prolonged hypoxia), alcohol abuse, and exposure to violent or traumatic head injury.

Specka et al. [205] assessed the performance of 54 methadone maintained patients and 54 controls matched for age, gender, and education on a battery of six cognitive-psychomotor performance tests. Attention and perception tasks were impaired in methadone patients. On a simple-choice reaction test, methadone patients showed higher speed in decision making and motor reaction but had an increase in decision errors. On a tracking test, methadone patients showed fewer deviations but required more time for the test. The patients did poorer at higher speeds. The authors felt that the observed variance was better explained by sociodemographic features than by belonging to the group of methadone patients and recommended that fitness to drive be determined individually.

## 2. Summary of Epidemiological Studies.

Blomberg and Preusser [20] gathered data on 1562 methadone maintenance patients in New York State through interviews and compared this data to that of a

control group of 1059 people. Driving records for 718 methadone patients and 579 control subjects were also obtained and analyzed. The driving records indicated no difference in violation rate between the groups. Accident rates of methadone patients compared favorably with New York drivers of similar age and sex.

Babst et al. [6] examined driving records of 448 New York State methadone maintenance patients and matched them to a sample of 182 male drivers in New York City. When compared by age group, conviction rate, accident rate and type of accident were about the same.

Maddux [143] compared driving records of 104 heroin addicts during the year prior to admission to a methadone maintenance program and during the one year after admission while they were maintained on methadone. A significant increase in speeding convictions during the year on methadone was found. Changes in convictions for negligent collision, other moving violations, or accidents were small and insignificant. The frequency that these subjects were involved in accidents did not differ significantly from that of all Texas licensed drivers.

Terhune et al. [216] collected blood specimens from 1882 drivers of passenger cars, trucks, and motorcycles who died within 4 h of a crash. Toxicology analysis identified 57.9% of the drivers as having at least one substance, alcohol or drug, detected. The prevalence rate of methadone was 0.1%.

Farrell and Cada [64] reported toxicology statistics for 1194 urine specimens submitted by Drug Recognition Experts collected over a two year period from subjects suspected of DUID. Narcotic analgesics were identified in 100 specimens (8.4%). Methadone was identified in 13 of these specimens. It was the only opioid identified in 7 of the 13 specimens.

Karlovesek [120] reviewed 462 cases submitted for toxicological examinations during the time period of 1991 and 1997. Traffic accidents had occurred in 36.6% and the remaining 63.4% were suspected of driving under the influence of drugs. One or more psychotropic drugs were found in 54.3% of the samples with 19.4% of these positive for methadone. In the samples from traffic accidents, methadone was the fifth most frequent drug found (17.2%). In the samples from suspected drivers, methadone was the third most common drug found (19.2%). Multiple drug use was frequently detected in the methadone positive samples. In only 14 out of 74 (18.9%) methadone cases was methadone the only drug identified. Opioids were found in 61% of the methadone positive cases, benzodiazepines in 29.7%, and cannabinoids in 22.9%. Current traffic legislation classifies driving under the influence of methadone prescribed by a doctor as a minor offense but methadone program subjects do not meet the health criteria required for obtaining a driver's license.

## IV. MORPHINE

Morphine is widely used in the management of moderate to severe pain. Multiple preparations are available for the administration of morphine by subcutaneous, intramuscular, intravenous, epidural, or intrathecal injection. Typical dose ranges are 1–10 mg/kg. Oral preparations are also available in standard release and extended release. Oral dosages range from 20–200 mg per day.

Morphine is the archetypical  $\mu$  receptor agonist. As such it produces antinociceptive response at both the spinal level and brain level. The side effects are the classic opioid effects of nausea, dry mouth, miosis, and constipation. Morphine is also usually referred to as a central nervous system depressant. However, opioids also have psycho-stimulant properties independent of any analgesic effects. For morphine, these effects appear to be primarily modulated by stimulation of dopamine release in the nucleus accumbens [46].

### A. Pharmacology and Pharmacokinetics

The serum half-life for morphine is about 3 h. **Table 7** contains reported serum concentration ranges after varying dosages. A single intramuscular 8.75 mg/70 kg dose resulted in a 0.070 mg/L peak serum concentration 10–20 min after dosing [16]. Vianio et al. [218] reported a steady-state blood morphine of 0.066 mg/L in cancer patients receiving 209 mg/day. Westerling et al. [225,226] reported 0.0071 mg/L serum morphine after a 10 mg IV dose.

Due to high first pass metabolism only 20–40% of oral morphine is bioavailable [225]. Approximately 5% of the dose is *N*-demethylated to form normorphine that does not appear to have pharmacological activity. The majority of morphine is conjugated to form morphine-3-glucuronide that then undergoes biliary excretion [11]. Up to 87% of a morphine dose is excreted in the urine with 75% present as morphine-3-glucuronide.

In vivo, M6G is much more active than morphine itself with an ED<sub>50</sub> for morphine of 928 ng and 7.3 ng for M6G [246]. Permeability of M6G may be greater than anticipated due to conformational forms of M6G that minimize polar group exposure [159]. This is contradicted by Wu et al. [239], who reported a 32 fold lower uptake of M6G into the brain than morphine.

Miosis, vomiting, unconsciousness, and respiratory depression classically indicate overdose of morphine. Doses greater than 30 mg parenterally or 100 mg orally can be toxic to a naïve adult. Doses of 120 mg may be lethal. One individual demonstrated blood concentrations of 0.62, 6.2, and 11 mg/L of morphine, morphine-3-glucuronide and M6G 60 h after a 5 g dose of extended release

**Table 7.** Overview of controlled administration studies of morphine with psychomotor and cognitive effects

Drug	Dose	Study group <sup>a</sup>	End point measured <sup>b</sup>	Effects	Ref.
Morphine	0, 0.214, 0.286, 0.357, 0.429 mg/kg orally	24/21 NU	AVLT, PMC, PASAT, SRE; 1.5 h	Reported tired and mental clouding; impairment on AVLT at high doses; no motor, perceptual impairment	[34]
Morphine (cocaine HCl)	0, 5, 10 mg/70kg IV; (0, 8, 16, 32 mg/70 kg)	9/0 U	PHYS, SRE; 0–110 min	Increased reporting of “sedated”; significant increase in heart rate, blood pressure; plasma levels with linear decrease from ~20–100 min	[67]
Morphine	0, 10, 15 mg orally	8/4 NU	CFF, SRE, word recall, recognition; 1–6 h	Significant reduced CFF, delayed word recall; 15 mg dose produced significant improvement in reaction time	[94]
Morphine; hydromorphone	0, 5, 10 mg/70kg IV; 0, 0.33, 0.65, 1.3 mg/70 kg IV	12/5 NU;	ARCI, VAS, DEL, MW, DSST, PHYS; 0–300 min	No psychomotor impairment for morphine, significant miosis, increased reported “feeling” drug effect; modest psychomotor impairment for hydromorphone	[100]
Morphine	20, 40, 80 ng/mL target plasma by infusion	15/0 NU	FT, isometric force control, COG; 60 min	Impaired isometric force control; impaired cognitive function	[123]
Morphine	30–150 mg/day	0/6	VAS, EPR, vigilance COG	Reduced pain response, improved cognitive status due to removal of pain stress	[141]
Morphine	10 mg 4 doses at 4 h intervals; 4 sessions orally	4/6 NU	CRT, CFF, word recall, number vigilance, SRE	Morphine improved accuracy on CRT; Subjective calmness; no impairment of psychomotor function	[166]
Morphine	0, 10, 30, 56, 100 mg orally	9/0 U	DSST, ARS, VAS, ARCI, PHYS; 0–4 h	Significant increases in subjective effects scales; significant dose dependent effect on DSST miosis heart rate, BP and skin temp	[173]
Morphine	209 mg/day mean orally	22/27	FT, PHYS, ART-90	No psychomotor hazards to traffic; slight dose dependent effect on tasks demanding concentration; plasma concentration of 66 ng/mL	[218]
Morphine, Codeine	0, 20, 40 mg morphine; 0, 60, 120 mg codeine orally	9/3 NU	Wartegg personality ARCI, PHYS, MW, DSST; 0–4 h	Plasma levels: codeine 52–256 ng/mL, morphine 12–50 ng/mL dose related miosis; no impairment by codeine or morphine	[222]
Morphine	0, 2.5, 5, 10 mg/70kg cumulative dosing IV	10/6 U	ARCI, VAS, DEL, MW, DSST, PHYS; 0–120 min	Mild but significant dose related effects	[223]
Morphine	10 mg IV; 20, 30 mg orally controlled release	6/4 NU	Salivation, CRT; 0–12 h	Prolonged CRT at ~7.1 ng/mL serum (after IV); significant decrease in saliva production for morphine	[225]
Morphine	0, 0.05, 0.1, 0.2, 0.3 mg/kg IV	4/2 NU	Pain threshold, reflex threshold	Dose dependant depression of nociceptive reflexes; depressive effect on nociceptive transmission at the spinal level	[228]
Morphine; butorphanol	0, 10 mg/70 kg IV; 0, 0.5, 1, 2 mg/kg IV	7/5	ARCI, VAS, DEL, MW, DSST, PHYS; 0–300 min	Morphine: no psychomotor impairment, significant miosis, increased “feeling” drug effect; dose related psychomotor impairment for butorphanol	[244]
Morphine (buprenorphine)	10 mg/70kg IV; 0, 0.075, 0.15, 0.3 mg/kg IV	11/5 NU	Same as above	Morphine: same as above; psychomotor impairment for buprenorphine	[240]
Morphine; nalbuphine	0, 10 mg/70 kg IV; 0, 2.5, 5, 10/70 kg IV	12/4 NU	Same as above	Morphine: same as above; psychomotor impairment for nalbuphine	[241]
Morphine; pentazocine	0, 10 mg/70 kg IV; 0, 7.5, 15, 30 mg/70 kg IV	12/4 NU	Same as above	Morphine: same as above; psychomotor impairment for pentazocine	[242]

<sup>a</sup> Number of subject studied: Male/female; NU: Non-user; U: User.

<sup>b</sup> AVLT: Rey Auditory Verbal Learning Test; PMC: Perceptual motor coordination tests, including pegboard tasks and trail making tests; PASAT: Paced auditory serial addition test; SRE: Self reported effects; PHYS: Physiological testing (varied combination of heart rate, blood pressure, skin temperature, etc.); CFF: Critical Flicker Fusion; ARCI: Subject effect questionnaire; VAS: Visual analog scale, rating of subjective effects; DEL: Drug effect/liking subjective effect survey; MW: Maddox-Wing Test; DSST: Digit symbol substitution test; FT: Finger tapping; COG: Cognitive functioning testing; EPR: Evoked potential response; CRT: Complex reaction time; ARS: Adjective rating scale; ART-90: Road safety test from Australia.

tablets [226]. Overdose responds well to supportive treatment and administration of naloxone [225,226].

## B. Reported Effects on Performance

### 1. Summary of Reports

Table 7 includes a summary of morphine related clinical studies and Table 4 includes prevalence and epidemiological studies pertaining to morphine usage and accident rates.

Cleeland et al. [34] administered 0, 0.214, 0.286, 0.357, and 0.429 mg/kg oral doses of morphine to 24 males and 21 females. As well as measuring analgesic effects, they measured memory and learning by the Rey Auditory Verbal Learning Test (AVLT). Motor coordination was measured with a pegboard task and trail making tests. Sustained mental attention was evaluated by the Paced Auditory Serial Addition Test (PASAT). They found that the highest doses of morphine resulted in impaired word recall, but did not produce any measurable impaired motor coordination by the tests used.

Foltin and Fischman [67] administered 0, 5, and 10 mg/70 kg doses of IV morphine both with and without the combination of 0, 8, 16, and 32 mg/70 kg doses of IV cocaine. Subjects included eight black and one white male volunteer with prior histories of cocaine and heroin use. Subjective effects were measured by several questionnaires including the ARCI questionnaire. A serial acquisition task was devised with a monetary reward system. Heart rate and blood pressure were also measured. Cardiovascular effects correlated more strongly with cocaine dosages alone. Morphine dosage alone increased opioid symptoms and ratings of "sedated". Both cocaine and morphine increased peak heart rate and blood pressure.

Hanks et al. [94] administered 0, 10, and 15 mg morphine IV to eight male and four female healthy volunteers. Cognitive function was measured by complex reaction time (CRT), number vigilance, memory scanning, word recall and recognition, picture recognition, and CFFT. Subjective measures of effect were also assessed. Subjective measures did not indicate a significant impairment of alertness. CFF was reduced for the observation period (6 h). The 15 mg dose of morphine produced a significant improvement in the CRT test.

Hill and Zacny [100] examined the effects of 0, 5, and 10 mg/70 kg morphine IV on the ARCI and other subjective effects tests of twelve males and five female volunteers. Psychomotor performance was measured by the MW test and the DSST. Heart rate, blood pressure, arterial oxygen saturation, and miosis were measured. Some subjective effects of morphine doses were reported but no psychomotor impairment was noted for morphine doses.

Kerr et al. [123] assessed effects of targeted plasma levels of morphine achieved by infusion pump administration to 15 male volunteers. Serum concentrations were maintained at 0.02, 0.04, and 0.080 mg/L for the study. Measured end-points included finger tapping rates and maintenance of isometric force with and without visual stimulus. Tests of verbal comprehension and memory were also performed. The ability to maintain low consistent levels of force decreased. Delayed recall of information during the morphine infusion was also impaired.

O'Neill et al. [166] found after repeated oral doses of morphine that the only significant effect was an increase in the accuracy of responses on a CRT. Four male and six female volunteers were administered 0 or 10 mg every 4 h on four separate days at least a week apart. Subjective effects were assessed as well as a variety of cognitive function tests.

Zacny's group at the University of Chicago [240–246] investigated a range of morphine dosages administered both IV and orally. Subjective effects were measured using the ARCI questionnaire and other questionnaires. Psychomotor performance was measured using the MW test, eye-hand coordination tests, auditory reaction times, and DSST. Physiological endpoints of heart rate, blood pressure, arterial oxygen saturation respiration rate, and miosis were measured. Overall, morphine dosages had a mild or no effect on cognition or psychomotor performance as measured.

Westerling et al. [225] administered a 10 mg morphine IV infusion, a 20 mg oral solution, or an extended release tablet of 30 mg to ten healthy volunteers. CRT and salivation were measured. Significant decreases in salivation were observed and increases in CRT times were related to plasma concentrations of morphine. The greatest effects were observed for the greatest plasma concentrations obtained by the IV infusion.

## V. OXYCODONE

Oxycodone, 14-hydroxy-7,8-dihydrocodeinone, is a semisynthetic narcotic analgesic derived from thebaine. Given subcutaneously, oxycodone is approximately equipotent to morphine and is prescribed for the relief of pain that requires treatment for more than a few days. Available for clinical use since 1915, oxycodone is marketed in many tablet, capsule, and liquid formulations, which contain from 2.25–5.0 mg of oxycodone. Many of these formulations also contain aspirin, phenacetin, or caffeine.

The medical use of oxycodone increased by 23% during the time period of 1990 to 1996. During the same time period, the reports of abuse decreased by 29% and the

estimated number of emergency department episodes were stable [112]. In 1996 a controlled-release preparation marketed as OxyContin was made available in 10, 20, 40, 80, and 160 mg strength. OxyContin tablets are taken every 12 h. This product has been the focus of drug abuse on the East Coast as it is reported to give a high very close to that of heroin. "Oxy" abusers will chew the tablets, crush the tablets, and snort the powder, or dissolve the oxycodone in water and inject the liquid for the maximum effect. Oxycodone abuse has been a problem since the 1960s but now a steady increase in Oxy addicts in methadone programs has been seen. The number of emergency department episodes involving oxycodone have dramatically increased since the release of OxyContin in 1996.

### A. Pharmacology and Pharmacokinetics

The most serious risk associated with oxycodone, as with other opioids, is respiratory depression with side effects typical of opioids. Immediate-release oxycodone produces a greater number of adverse side effects than controlled-release oxycodone. Severe withdrawal includes flu-like symptoms, vomiting, and body aches, which can last for a few weeks.

With intravenous administration the relief of pain is immediate, within 5–8 min, and lasts for approximately 4 h. Assuming complete absorption after intramuscular administration, oral oxycodone has a bioavailability of 60% [178]. This is a higher oral bioavailability than morphine and is believed to be due to the 3-methoxy substitution that prevents extensive first-pass glucuronidation. Time to  $C_{max}$  ranges from 1–1.5 h. Mandema et al. [145] demonstrated that the absorption profile of the controlled-release oxycodone tablets begins with a rapid absorption component ( $t_{1/2abs} = 37$  min) that accounts for 38% of the available dose. This is followed by a slow absorption phase ( $t_{1/2abs} = 6.2$  h) that accounts for the remaining 62% of the dose. Two 10 mg tablets of oral controlled-release oxycodone hydrochloride were found to be 102.7% bioavailable relative to 20 mg of immediate-release oxycodone hydrochloride oral solution. The controlled-release tablets allow an effective plasma concentration of oxycodone to be reached quickly and for this effective concentration to be maintained for a longer period of time than with immediate-release oxycodone allowing for dosing every 12 h. Unlike immediate release formulations, controlled-release oxycodone was also shown to be bioequivalent under fed and fasted conditions [14]. Rectal administration, with a mean bioavailability of 61% [134], results in a delayed relief of pain, 0.5–1.0 h, but also provides a longer duration of analgesia ranging from 8–12 h. Oxycodone can also be administered intranasally, where

it is rapidly and effectively absorbed from the nasal mucosa. The mean bioavailability has been shown to be 46% but had wide variation limiting its clinical usefulness. Mean elimination half-life ranges from 2–5.5 h with marked interindividual variation [133,134,179,214].

Plasma concentrations following a single oral dose of 4.5 mg reached a peak of 0.009–0.037 mg/L [189]. Dosing with 20 mg controlled-release oxycodone resulted in a mean  $C_{max}$  of 0.0186 mg/L at 2.62 h while dosing with 20 mg of immediate-release oxycodone resulted in a mean  $C_{max}$  of 0.0416 mg/L at 1.30 h [145]. A similar  $C_{max}$  of 0.0204 mg/L, 0.0232 mg/L, and 0.0201 mg/L after a dose of 20 mg controlled-release oxycodone were reported respectively by Heiskanen et al. [98] Kaiko et al. [113] and Benziger et al. [15]. Using an intramuscular dose of 0.14 mg/kg oxycodone hydrochloride, Poyhia et al. [180] reported a  $C_{max}$  of 0.034 mg/L and a  $C_{min}$  of 0.038 mg/L for a 0.28 mg/kg oral dose.

Nine deaths involving oxycodone were investigated by Drummer et al. [50]. All deaths gave femoral blood concentrations, ranging from 0.6–1.4 mg/L (mean 0.90 mg/L), that were higher than that expected following normal therapeutic use. Other drugs were detected in all cases. The presence of oxycodone was given as a factor contributing to death in all of the cases.

Oxycodone is metabolized in the liver through *N*- and *O*-demethylation, 6-ketoreduction, and conjugation with glucuronic acid. The *O*-demethylation reaction is catalyzed by the enzyme cytochrome P450 2D6 (CYP2D6) with the end product of oxymorphone, an analgesic that has a potency approximately 10 times that of morphine. The resulting plasma concentration of oxymorphone is very low in comparison to that of oxycodone; therefore, oxymorphone is not responsible for the analgesic effect of a dose of oxycodone [98,113]. *N*-Demethylation results in noroxycodone that has only weak affinity for the  $\mu$ -opioid receptor. If the action of CYP2D6 is blocked, the concentration of noroxycodone increases as oxymorphone decreases [98]. 6-Keto reduction results in the formation of 6-oxycodol.

Eight to 14% of the dose of oxycodone is excreted in the urine as unconjugated and conjugated oxycodone over a 24 h period. Oxymorphone is excreted mainly as a conjugate, noroxycodone is found mostly in unconjugated form. Noroxycodone concentrations in plasma and urine were found to be higher after oral administration when compared to intramuscular administration [180].

The pharmacokinetics of oxycodone and noroxycodone showed no significant differences between young men, young women, elderly men, and elderly women. Differences in the pharmacokinetic profile of oxymorphone were observed between these four groups [114].

## B. Reported Effects on Performance

### 1. Summary of Clinical Studies

Saarialho-Kere et al. [196] administered 0.13 mg/kg oxycodone by intramuscular injection to nine healthy male and female volunteers ages 20–26. Post-drug test times were at 1.5, 3, and 4.5 h and included several psychomotor function tests, subjective assessments, and the measurement of ventilatory function. The psychomotor skills were evaluated using the DSST, the CFF, MW, tapping test, a divided attention test, a tracking and choice reaction time test. Effects on performance peaked at 1.5 h with prolonged reaction time and impaired vigilance, attention, body balance, and coordination of extraocular muscles. Subjects assessed themselves as mentally slow and impaired 3 h after dosing. Critical flicker discrimination was impaired and some respiratory depression was still present at 4.5 h after administration. Mean plasma levels of oxycodone were 0.0095 mg/L at 45 min, 0.0220 mg/L at 1.5 h, and 0.0112 mg/L at 3 h.

Poyhia et al. [178] administered 19.6 mg/70 kg oxycodone to nine healthy young adults. The subjects were evaluated using MW, DSST, CFF, pupil size, and self-evaluation of sedation prior to dosing and at 1, 2.5, 5, and 8 h after dosing. Decremental effects were noted on all measures with maximal miosis at 1 h. Impairment on the CFF test and sedation persisted for up to 5 h.

Heiskanen et al. [98] administered 20 mg controlled-release oxycodone to ten healthy male and female volunteers ages 19–29. Psychomotor function was evaluated using the MW, DSST, CFF. Pupil size was measured. Subjective symptoms were evaluated with visual analog scales and a specific drug effect questionnaire. Blood samples were collected prior to drug administration and from 0.5–24 h after dosing with the mean peak plasma concentration of 0.0204 mg/L occurring at 2.25 h. Of all the psychomotor function tests, pupil size and MW were the only two correlated with the plasma drug concentration. Marked drowsiness and adverse performance on the CFF test occurred.

A dose-related decrease in pupil size was also documented by Pickworth et al. [174] and Kaiko et al. [113].

### 2. Summary of Epidemiological Studies

Farrell and Cada [64] reported toxicology statistics for 1194 urine specimens submitted by Drug Recognition Experts collected over a two-year period from subjects suspected of DUID. Narcotic analgesics were identified in 100 specimens (8.4%). Oxycodone was identified in four of these specimens. In one specimen morphine was also present and in another propoxyphene was identified in addition to the oxycodone.

## CONCLUSION

With opioids, the indications of impairment are mixed. In naïve users, some opioids have limited impact on fine motor coordination tasks. The results for cognitive testing indicate a decrement in recall tasks and vigilance tests. However, some cognitive tests are actually improved. Individuals typically reported experiencing effects of the drug even in cases where no impact on performance was measurable. Kerr et al. [123] provides some of the most substantial evidence of morphine impairment that pertains to driving with their unique testing of the ability to maintain low, consistent isotonic pressure.

The experience of the user with morphine has a dramatic effect on morphine impairment. Many authors find that personality modulates effects of other opioids as well. With many opioids, pain control in the individuals improves performance potentially by reducing distractions. Lorenz et al. [141] also found that patients chronically treated with morphine demonstrated little or no impairment when measuring several evoked potential endpoints. These aspects of opioid effects complicate the interpretation of samples collected for impaired driving and merits consideration.

The effects of methadone on driving performance are summarized well by Friedel and Berghaus [72]. “Heroin addicts treated with methadone are generally not fit to drive. A positive evaluation might be possible in exceptional cases when there are special circumstances justifying it. Among these are, for instance, a period of methadone substitution of more than a year, stable psychological integration, no evidence of the consumption of additional psychotropic substances, including alcohol, evidence of a subject’s readiness to feel responsible for himself/herself and of therapy compliance, and no evidence of serious defects of the personality as a whole. The opinion of the physicians treating the patients also needs to be considered in the evaluation of each case.”

In determining impairment, serum or blood concentrations are the most appropriate for interpretation. These levels have the most relevance to effects of the drug at the time of sampling. Urine samples are an excellent indicator of recent exposure to the drug. Urine samples are not an adequate indicator of impairment at the time of sampling and back calculation of concentrations has limited merit due to the large number of factors confounding urinary excretion profiles. Opioid urinary values are also confounded by the potential for morphine and codeine to be present in poppy seeds in significant concentrations [110]. Additionally, several opioid compounds have similar metabolites and may produce similar urinary profiles depending on when in the overall excretion a sample is collected. Thus, confounding the interpretation [73].

Hair samples are a reasonable indicator of exposure to opioids. Hair has the likelihood of providing information about historical exposure and a longer detection window for exposure than other matrices. However, no significant dose response relationship has been established for hair samples. Hair cannot indicate if an individual was impaired or the timing of dosage with more accuracy than to within weeks to months. All such factors should be considered in the interpretation of impairment.

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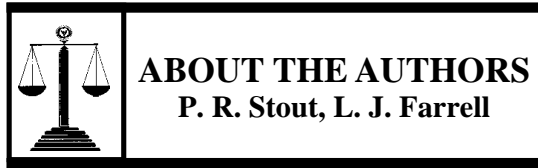
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### APPENDIX — LIST OF ABBREVIATIONS

- ARCI** — Subjective effect questionnaire.
- ARS** — Adjective rating scale.
- ART-90** — Road safety test from Australia.
- AVLT** — Rey Auditory Verbal Learning Test.
- BAC** — Blood alcohol concentration.
- CFF** — Critical Flicker Fusion.
- CMI** — Cornell Medical Index.
- COG** — Cognitive functioning testing.
- COT** — Cross-Out Test.
- CRT** — Complex reaction time.
- CTT** — Complex tracking task.
- DEL** — Drug Effect/Liking subjective effect survey.
- DRE** — Drug recognition expert.
- DS** — Driving simulator.
- DSST** — Digit symbol substitution test.
- DVA** — Dynamic visual acuity.
- EPR** — Evoked potential response.
- FT** — Finger tapping.
- HWT** — Hidden Word Test.
- MAACL** — Multiple Affect Adjective Checklist.
- MM** — Methadone maintenance subject.
- MW** — Maddox-Wing test.
- PASAT** — Paced auditory serial addition test.
- PHYS** — Physiological testing, varied combinations of heart rate, blood pressure, skin temperature, etc.
- PMC** — Perceptual motor coordination tests, including pegboard tasks and Trail making tests.
- SRE** — Self reported effects.
- VAS** — Visual analog scale, rating of subjective effects.
- VMC** — Visuomotor coordination test.
- VST** — Visual search task.
- WAIS** — Weschler Adult Intelligence Scale.



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