Syva Emit II Plus Buprenorphine Assay

Compliance Monitoring in Medically Assisted Opioid Addiction Treatment

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Introduction

Worldwide opioid addiction has increased dramatically in the last decade, with the greatest rise documented in the U.S.[1-3] A primary factor driving this growth is the increasing use of prescription opioids (e.g., oxycodone, hydrocodone, and morphine) for chronic pain in response the American Pain Society's assertion that pain should be assessed as the "fifth vital sign" in outpatient care.[4,5] Recreational use of heroin also continues to contribute to opioid addiction. In the U.S. alone, heroin use almost doubled between 2002 and 2014, from 1.6/1000 persons ≥12 years of age to 2.6/1000 persons. Illegally obtained prescription opioids serving as gateway drugs attribute to approximately 80% of this population.[2] Conversely, previous heroin use accounts for only 20% of prescription opioid abuse.[2]

Opioid Chemistry and Physiologic Effects

Opioid drugs are derived from the opium poppy, Papaver somniferum. First cultivated by the Sumerians and named "Hul Gil" (the joy plant), opium and derivative drugs have been used for over five millennia, both medically (analgesia, sedation) and recreationally (euphoria).[6] Naturally derived and semisynthetic opioids share a similar structure, while synthetic opioids do not (Figure 1).[7] Their primary agonist targets are mu receptors. These drugs can also cause depressed respiration, slowed or rapid heart rate, and reduced gastric motility.[7] Overdose due to cardio-pulmonary effects can be fatal.

All opioid effects are in response to drug stimulation of mu receptors, which are found in the brain, spinal cord, and gastrointestinal tract. The natural mu receptor agonist is β-endorphin ("endogenous morphine"), a 31-amino acid neuropeptide/neurohormone.[8,9] When released in the central nervous system (CNS), β-endorphin interacts with the mesolimbic reward system. This system uses positive reward to reinforce learning and behavior necessary for survival. When β-endorphin activates the mu receptor in response to enjoyable input, dopamine is released and stimulates specific brain loci. Some of these loci trigger sensations of pleasure and desire, while others evaluate the benefit of repeating the behavior. When it interacts with synapses in the peripheral nervous system (PNS), β-endorphin acts as a natural pain killer. Feeling "normal" depends on regular low-level stimulation of PNS mu receptors by β-endorphin, and without it, even a minor injury such as a stubbed toe would register as incapacitating pain.[8,10,11]

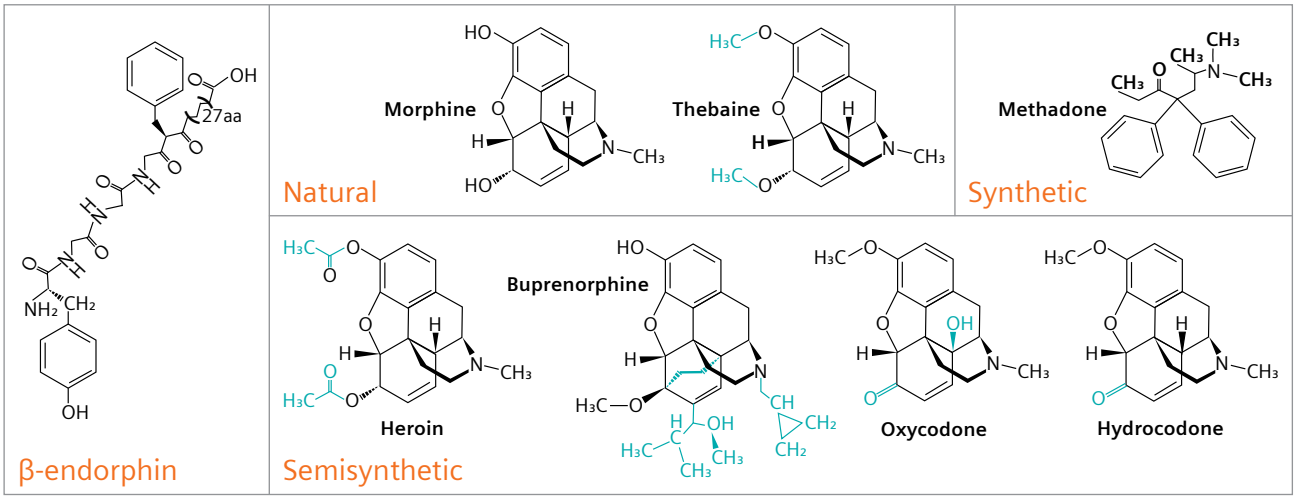

Figure 1. Structural similarity between β-endorphin and natural and synthetic opioids.
Red indicates how each natural or semisynthetic molecule differs from morphine.

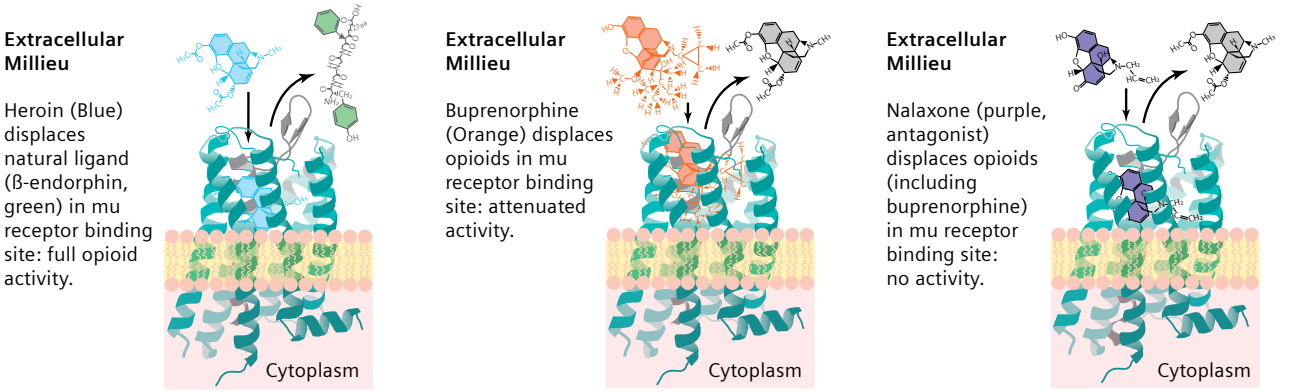

Figure 2. Agonist and antagonist binding at the mu receptor.[23]

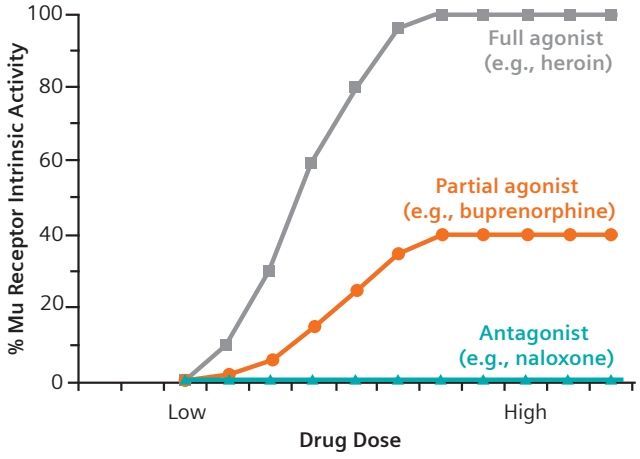

Figure 3. Mu receptor activity depending on ligand.[22]

Addiction

Hijack of the CNS and PNS mu receptor functions by either prescription or illicit opioids can cause addictive behavior in genetically and environmentally susceptible individuals.[10,12,14] Opioid addiction includes both physiologic drug dependence (drug is needed to replace non-pain-related PNS stimulation by β-endorphin) and physical and psychological cravings (CNS loci associated with cravings and reward value require constant stimulation). Tolerance develops with continued drug use, requiring ever-increasing dosage to achieve both euphoric effects and feelings of physical normalcy. Because most opioid drugs are short-acting, with effects lasting from only a few hours to 8 hours, addicted users cycle constantly through peaks of physical well-being and valleys of minor to severe withdrawal symptoms.[7,15] Continued use of opioids—especially pharmaceuticalgrade opioids—can result in changes to brain chemistry and morphology, resulting in down-regulation of ß-endorphin synthesis and increasing or total dependence on exogenous drugs.[10,13]

Medically Assisted Opioid Addiction Therapy

Because of damage caused to the normal endorphin-producing cells, opioid addiction is considered a chronic brain disease and may require lifelong drug treatment and management.[16] Medically assisted therapy (MAT) uses drugs such as buprenorphine (BUP) to prevent the negative symptoms of withdrawal and ease dependency and cravings until normal brain chemistry is restored, if possible.[16-19] MAT is a more effective option for treating addiction than methods that do not employ medication.[15,17,20,21]

BUP is derived from the natural opium alkaloid Thebaine (Figure 1). As a partial mu agonist, BUP has high affinity for the mu receptor, preferentially binding to it over other opioids.[15,22,23] It both displaces other opioids bound by receptors and prevents new molecules from binding (Figure 2).[23] Because it has low physiological activity, euphoric effects are minimized when taken as intended (Figure 3).[7,19,24,25] The "high" associated with other opioids diminishes rapidly with repeated administration of sublingual or transdermal BUP and cannot be induced by taking increasing doses when administered correctly (ceiling effect).[24] This ceiling effect also reduces the risk of respiratory depression, bradycardia, and overdose.[19]

Despite this, BUP itself is subject to abuse through diversion (circumvention) of the drug's appropriate use. Diversion includes inappropriate drug administration (inhaling, smoking, or injection), selling prescribed pills to purchase other opioids (potentially because treatment dose is insufficient, especially in early treatment), and skipping doses to take other opioids.[1,5,26-30] Other predominant reasons include sharing prescriptions with others who don't have access to care and are trying to self-treat, hoarding pills to use at a higher dosage, and selling a portion of the prescription to finance addiction treatment costs.[5,27,31-34] BUP combined with naloxone (trade name SUBOXONE) reduces—but does not eliminate—diversion risk by inhalation or injection because administration of naloxone by these methods causes immediate and severe withdrawal symptoms.[28,31-33]

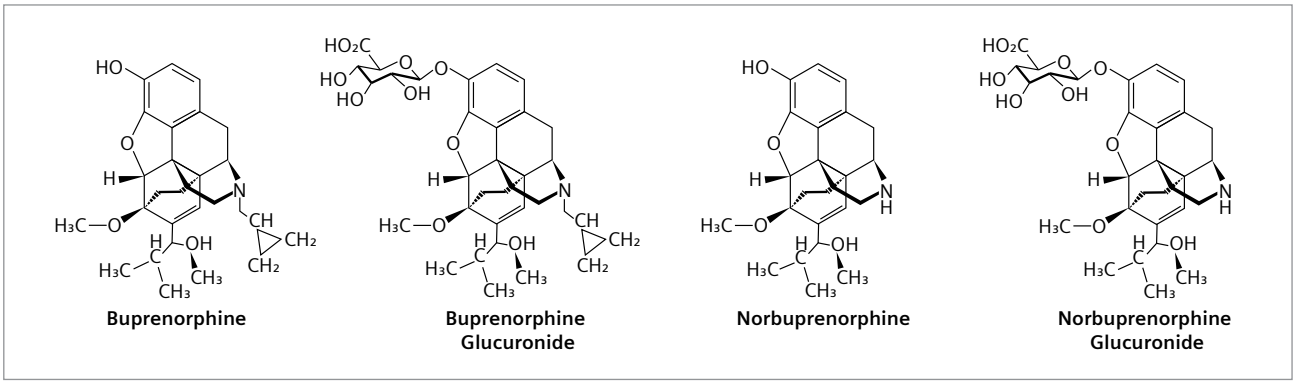

Figure 4. BUP and its major metabolites.[42,44]

Buprenorphine Testing

Buprenorphine urine testing is valuable both clinically and in the emergency department when screening for abused substances. The American Society of Addiction Medicine (ASAM) recommends urine drug testing throughout MAT to assess compliance and promote longterm recovery: more frequent testing is suggested during early treatment and if the patient relapses.[15,18,35,36] Patients treated in opioid treatment programs (OTP) must be administered at least eight drug tests annually according to U.S. federal law, but no recommendations exist for treatment through a private physician's office. Oral BUP is prescribed both on- and off-label for chronic pain control in many countries, and periodic random monitoring is also suggested.[36-38]

Because of their low cost, easy accessibility, and high throughput, immunoassays (IAs) are useful for primary screening. Urine concentration of BUP may be below the detection limit of most assays, therefore assays are designed to detect BUP and at least one of its three major metabolites: norbuprenorphine (norBUP), buprenorphine glucuronide (BUP-G), and norbuprenorphine glucuronide (norBUP-G). These metabolites (Figure 4) are typically excreted in urine at concentrations many times greater than the parent drug (Figure 5).[35,39-47] Furthermore, urinary levels of the parent drug can decline appreciably in a matter of hours, which can make identification difficult in an emergent situation; however all three metabolites can be detected in the absence of BUP and remain detectable for at least 4 days after sublingual administration (Figure 6).[40,42-45,48] Gas (GC) or liquid (LC) chromatography followed by tandem mass spectrometry (MS/MS) is used to confirm IA results and to determine the ratio of NorBUP:BUP as an indicator of sample adulteration (addition of crushed BUP).[35,43,49]

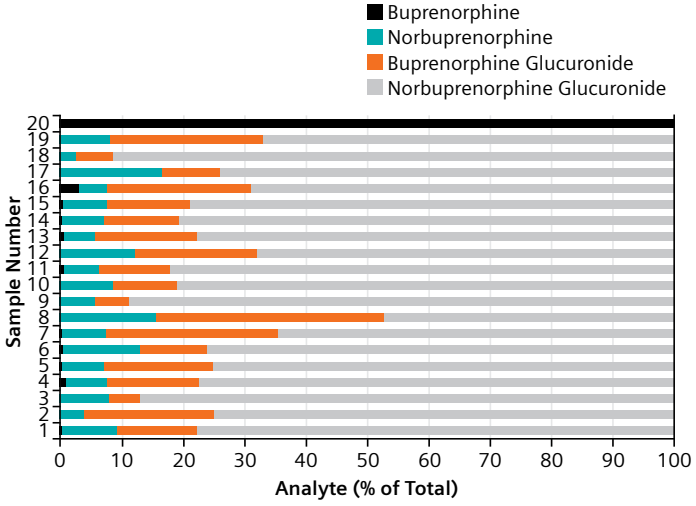

Figure 5. Percentage of BUP and major metabolites measured using LC/high-resolution MS in the urine of 20 MAT patients. The sample containing only BUP indicates probable adulteration with crushed drug (adapted from Belsey, et al.).[40]

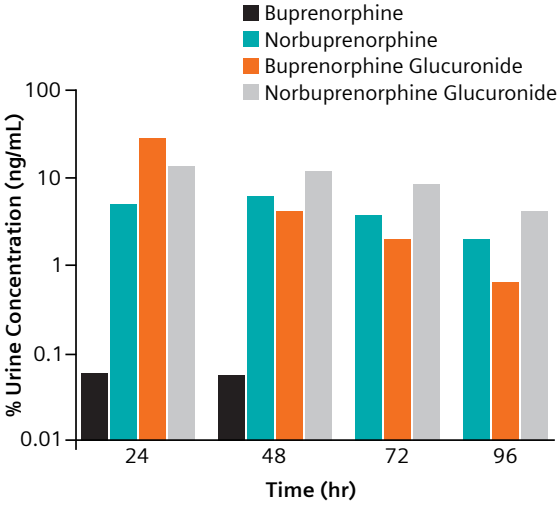

Figure 6. Changes in urine BUP and norBUP determined using LC/MS/MS in a single subject following ingestion of a single 2 mg dose of BUP (adapted from Regina, et al.).[45]

The Siemens Healthineers Assay and Assays from Other Manufacturers

The Siemens Healthineers Syva® Emit® II Plus Buprenorphine Assay for the Viva™ Drug Testing Systems detects both BUP and norBUP. Results can be reported both qualitatively and semiquantitatively based on a 5 ng/mL cut-off.[50] For both usages, positive agreement (PA) between the assay and LC/MS/MS is 90% and negative agreement (NA) is 98%.[51]

Four other commercial BUP IAs are currently available. All four can be used either qualitatively or semiquantitatively, and all show good positive and negative agreement with tandem mass spectrometry according to their package inserts (Table 1).[52-55] The Siemens Healthineers assay performs at least comparably to all of these assays with respect to positive and negative agreement with tandem mass spectrometry, and its detection cutoff is lower than either the Lin-Zhi EIA or Thermo Fisher CEDIA Buprenorphine II assays. Although positive agreement with LC/MS/MS is lower for the Siemens Healthineers assay than reported by other manufacturers, this is because we chose to challenge the assay by testing many samples having a BUP concentration very close to the 5 ng/mL cutoff.

Because of the structural similarity between BUP and other opioids, high antibody specificity for BUP and its metabolites is necessary to reduce the likelihood of falsepositive results. Twenty-two common opioids and metabolites demonstrated <0.01% cross-reactivity with the Emit assay at a concentration of 100,000 ng/mL. In addition, a wide range of structurally unrelated compounds and over-the-counter medications did not interfere with assay results above the 5 ng/mL cutoff.

In contrast, several independent evaluations of the original CEDIA assay conducted between 2005 and 2014, including information reported by the manufacturer, indicated up to 40% cross-reactivity with other opioids and structurally dissimilar and unrelated drugs at therapeutic levels (e.g., antimalarial/immune modulators chloroquine and hydroxychloroquine and antipsychotics sulpride and amisulpride).[41,44,46,56-59] Detection of these compounds generated false-positive results above the 5 ng/mL cutoff. While specificity of the newly released CEDIA Buprenorphine II assay has improved, it comes at the expense of sensitivity. The cutoff for this new assay has been increased to 10 ng/mL.[55]

Table 1. Commercially available BUP immunoassays. Unless specifically cited, all information was obtained from each manufacturer's package insert or data sheet.

				MS/MS Agreement					
				Qualitative		Semi-Quantitative		Tests within 50% above the cut-off: (Range – ng/mL) (%) (Total Pos/Total)	
Manufacturer/ Assay Name	Metabolites Detected (cross-reactivity)	Cut-off (ng/mL)	Measurable Range (ng/mL)	Pos (%)	Neg (%)	Pos (%)	Neg (%)	Qualitative	Semi-Quantitative
Siemens Healthineers Emit II Plus Buprenorphine Assay	BUP (100%) norBUP (92.6%) BUP-G (0.1%) norBUP-G (0.1%)	5	0.7–25	90	98	90	98	5.0–7.5 94.1 16/17	5.0–7.5 94.1 16/17
Thermo Fisher (Microgenics) CEDIA Buprenorphine Assay	BUP (100%) BUP-G (98%) norBUP (<0.015%) norBUP-G (<0.015%)	5	1.25–75	100	98	N/A[a]	N/A	N/A	N/A
Thermo Fisher (Microgenics) CEDIA Buprenorphine II Assay	norBUP (125%) BUP (100%) norBUP-G (100%) BUP-G (76.9%)	10	Not specified – 100	98.9[b]	100	100[b]	100	10–15.0 100 5/5	10–15.0 100 5/5
Lin-Zhi International, Inc. Buprenorphine Enzyme Immunoassay (EIA)	norBUP (100%) BUP (94.3%) norBUP-G (0.97%) BUP-G (0.03%)	10	3–70	97.4	95.3	N/A	N/A	10–15.0 75 6/8	N/A
Immunalysis Buprenorphine Homogeneous Enzyme Immunoassay (HEIA)	BUP (100%) norBUP (90.91%) BUP-G (0.17%) norBUP-G (0.13%)	5	0.6–40[c]	100	100	100	100	5.0–7.5 100 4/4	5.0–7.5 100 4/4

a. N/A indicates information is not available.
b. Includes contribution of measured metabolites
c. LoD per Belsey et al.40 to high calibrator from package insert.

Direct Comparison of the Siemens Healthineers Emit Assay to the Immunalysis HEIA Assay

A head-to-head comparison study was conducted between the Siemens Healthineers Emit and Immunalysis HEIA assays (Table 2).[60] Overall agreement was 92%. Negative agreement was 100% when compared both qualitatively and semiquantitatively. Positive agreement was lower at 87% due to eight discordant samples that were negative according to the Siemens Healthineers assay and positive according to HEIA. Upon further analysis using ID-LC/MS/MS, all eight samples were found to be negative and therefore in agreement with the results obtained with the Siemens Healthineers assay (Table 3). It is possible that this difference reflects slightly higher cross reactivity for norBUP by the Siemens Healthineers assay. Regardless, these data suggest that the Siemens Healthineers assay performs at least as well as the Immunalysis assay.

Summary

- The opioid epidemic presents an ongoing worldwide health crisis. Opioid addiction is difficult to overcome without the aid of medically assisted therapy.
- Buprenorphine is a partial mu agonist used in medically assisted therapy, and random periodic urine testing is recommended to assess compliance and correct dosing.
- Buprenorphine immunoassays provide only a preliminary analytical test result. A more specific alternative chemical method must be used to obtain a confirmed analytical result. Gas chromatography/tandem mass spectrometry (GC/MS) or liquid chromatography/mass spectrometry (LC/MS/MS) are the preferred confirmatory methods.
- Immunoassays should be able to detect buprenorphine and some combination of its metabolites at a sensitivity that shows good positive agreement with mass spectrometry.
- Immunoassays should be highly specific to reduce false positives resulting from cross-reactivity with other structurally similar opioids and structurally dissimilar non-opioid drugs that might be taken during therapy.
- The Siemens Healthineers Emit II Plus Buprenorphine Assay is both sensitive and specific, and demonstrates good positive and negative agreement with LC/MS/MS and the Immunalysis HEIA assay.

Table 2. Comparison of the Siemens Healthineers Emit assay to the Immunalysis HEIA assay.

		Siemens Healthineers Emit Assay				
		Neg (< 2.5 ng/mL)	Neg Within 50% below the Cut-off (2.5–4.9 ng/mL)	Pos Within 50% above the Cut-off (5.0–7.5ng/mL)	Pos (> 7.5 ng/mL)	% Agreement
Qualitative	Immunalysis Pos	0	8	11	43	87
	Immunalysis Neg	35	3	0	0	100
Semiquantitative	Immunalysis Pos	0	8	11	43	87
	Immunalysis Neg	35	3	0	0	100

Table 3. ID-LC/MS/MS evaluation of discordant results.

	ID-LC/MS/MS results (ng/mL)			Siemens Healthineers Emit Assay (ng/mL)	Immunalysis HEIA (ng/mL)	Final Interpretation		
Sample ID	BUP	norBUP	Total			ID-LC/MS/MS	Emit	HEIA
1	0	4.23	4.23	4.8	7.1	Neg	Neg	Pos
2	0	4.24	4.24	4.9	7.2	Neg	Neg	Pos
3	0	3.50	3.50	3.9	5.6	Neg	Neg	Pos
4	0	4.02	4.02	4.8	7.3	Neg	Neg	Pos
5	0	3.04	3.04	3.5	5.2	Neg	Neg	Pos
6	0	3.06	3.06	3.5	5.5	Neg	Neg	Pos
7	0	3.65	3.65	3.8	5.7	Neg	Neg	Pos
8	0	4.15	4.15	4.9	7.3	Neg	Neg	Pos

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An estimated 5 million patients globally benefit every day from our innovative technologies and services in the areas of diagnostic and therapeutic imaging, laboratory diagnostics, and molecular medicine, as well as digital health and enterprise services.

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