

Appendix 4: Methadone and buprenorphine pharmacology

	Methadone	Buprenorphine
Peak Plasma Conc	<ul style="list-style-type: none"> Four hours after regular oral administration (Range two to six hours) 	<ul style="list-style-type: none"> 90 to 150 minutes after regular sublingual administration.
Peak Clinical Effects	<ul style="list-style-type: none"> Two to six hours post oral dose (two to four hours first dose) Takes four to five days for methadone tissue plasma levels to stabilise, though accumulation continues beyond this, finally reaching a steady state after ten days. Once at steady state variations in blood concentrations are small. 	<ul style="list-style-type: none"> One to four hours post sublingual dose. It takes three to four days for buprenorphine plasma levels to stabilise.
Duration of action (half life)	<ul style="list-style-type: none"> The length of time it lasts in the body varies. Single dose; shorter half-life than maintenance dosing 12 – 18 hours means 15 hours. First few days between 13 and 112 hours mean 37 hours. Because of its cumulative effect until steady state is reached, methadone induction should be a cautious and gradual process. Elimination half-life is normally 20 – 37 hours but can range up to 91 hours for some individuals; its rate of clearance from the body can vary by a factor of almost 100. Optimal doses are usually between 24 – 36 hours. 	<ul style="list-style-type: none"> Related to dose. Low dose (e.g. 2 to 4 mg) may exert clinical effects for only a few hours, up to a maximum of 12 hours, because receptor occupancy will be minimal and plasma concentrations suboptimal. Higher doses (e.g. 16 to 32 mg) can exert effects for up to 48 to 72 hours. Optimal doses are usually between 24 and 36 hours. Elimination half-life is between 20 and 37 hours.
Metabolism	<ul style="list-style-type: none"> Well absorbed from the gastrointestinal tract into the blood stream Well distributed in body fats Metabolised through the liver via cytochrome P450 sub family of enzymes, thus susceptible to pharmacokinetic interactions with drugs that inhibit or induce liver enzymes. Binds well to plasma proteins and to lungs, liver and kidney tissues. Varies enormously in different people and widely different doses of methadone are needed to create the same serum methadone level. 	<ul style="list-style-type: none"> Principally in the liver via two hepatic pathways: glucuronide conjugation and N-dealkylation by the cytochrome P450 enzyme system. The tablets are administered sublingually because it has poor bioavailability. It is inactivated by gastric acid and has a high first pass metabolism.
Excretion	<ul style="list-style-type: none"> Excreted in the faeces and urine; urinalysis is useful only in confirming if being taken, but not establishing the dose. 	<ul style="list-style-type: none"> Excreted in the faeces and urine; urinalysis is useful only in confirming if being taken, but not establishing the dose.
Dosing	<ul style="list-style-type: none"> While research evidence suggests that optimal doses for most people lie between 60 and 120 mg some people will need more and some people will need less due to a range of individual factors such as size, gender, age, other health problems and metabolic clearance rates. Doses between 10 and 120 mg may exert clinical effects for 24 to 36 hours; low doses exert clinical effects for only a few hours. 	<ul style="list-style-type: none"> Maintenance is between 8 and 32 mg daily but the blockade dose (dose where the effects of additional opioids are markedly reduced) is maximal above 16mg daily.
Equivalence	<ul style="list-style-type: none"> Direct equivalence to street heroin is difficult to estimate, as purity of street heroin can vary (between 20 and 60%). One gram of street heroin is usually very roughly equivalent to 50 to 80 mg methadone. Direct equivalence of methadone and buprenorphine and vice versa is difficult to estimate, as the pharmacological properties of the two agents are not identical and it is not a linear relationship. When comparing the efficacy of maintenance doses, 50 to 80 mg methadone is approximately as effective as 12 to 16 mg buprenorphine in reducing heroin use and retaining patients in treatment. When comparing the equivalence of methadone to injectable pharmaceutical diamorphine, half-lives must be taken into consideration. This is not a linear relationship, so equivalence can vary from a methadone: diamorphine relationship of 1:3 (or even 1:1 for very low doses) to around 1:5 for high doses of diamorphine (e.g. 120mg methadone is equivalent to between 360 and 600mg of injectable diamorphine). 	<ul style="list-style-type: none"> Direct equivalence of methadone and buprenorphine and vice versa is difficult to estimate, as the pharmacological properties of the two agents are not identical and it is not a linear relationship. When comparing the efficacy of maintenance doses, 50 to 80 mg methadone is approximately as effective as 12 to 16 mg buprenorphine in reducing heroin use and retaining patients in treatment.
Tolerance	<ul style="list-style-type: none"> Develops at different speed in different individuals, can change in individuals over time and develops differently for different effects. With long term use, and in response to continued exposure of the brain to opiates, neuro adaptation occurs and involves changes in nerve and receptor function. Level of heroin use is not the only factor in determining the final dose of substitution that will be required. Patients react differently: some will need more and some will need less than others using the same amount of heroin. 	<ul style="list-style-type: none"> Develops at different speed in different individuals, can change in individuals over time and develops differently for different effects. With long term use, and in response to continued exposure of the brain to opiates, neuro adaptation occurs and involves changes in nerve and receptor function. Level of heroin use is not the only factor in determining the final dose of substitution that will be required. Patients react differently: some will need more and some will need less than others using the same amount of heroin