# Pharmacokinetics for psychiatrists

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**Abstract**

Pharmacokinetics describes the action of the body on administered drugs. This contribution illustrates that an understanding of pharmacokinetic principles is important in rational drug prescribing in psychiatry. Examples are presented to underline the clinical relevance of the important aspects of pharmacokinetics, encompassing drug absorption, distribution, phase I and phase II metabolism and excretion. Particular emphasis is placed on drug metabolism in the liver due to the prominence of cytochrome P450 enzymes such as CYP2D6, CYP3A4 and CYP1A2 in the phase I metabolism of psychotropic drugs. The concept of drugs being enzyme substrates, inhibitors (e.g. paroxetine for CYP2D6, fluvoxamine for CYP1A2 and fluoxetine for CYP3A4 and CYP2D6) and inducers (e.g. carmbamazepine with respect to CYP3A4) are discussed and the ramifications of P450 interactions for clinical practice examined. The potential impact of genetic polymorphisms on drug-metabolizing enzyme activity, such as that for CYP2D6, is also considered. In discussing renal excretion of psychotropic drugs, the impact of changes in lithium clearance, either through declining renal function or co-prescription of interacting drugs, is highlighted. This contribution also outlines further key concepts in pharmacokinetics which are relevant to clinical psychiatry – 'half-life', 'steady state', 'area under the curve' and 'bioavailability'. Finally, of particular importance when prescribing psychotropic drugs to elderly populations, the changes in drug handling that occur with advancing age are discussed.

**Keywords** absorption; CYP2D6; CYP3A4; drugs; elderly; inhibition; interaction; lithium; metabolism; pharmacokinetics; psychotropic drugs

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Pharmacokinetics describes the action of the body on administered drugs, including their absorption, distribution, metabolism and excretion. (In contrast, 'pharmacodynamics' describes the action of drugs on the body – see pages 263–267.) Pharmacokinetics is important in psychiatry for a number of reasons.

- Knowledge of drugs' absorption and distribution profiles allows prediction of the extent to which drugs can enter the body and reach their intended target organ, usually the brain.
- An understanding of the concepts of drug half-life and steady state allows rational dosing schedules to be implemented.
- Hepatic cytochrome P450 enzymes are responsible for the metabolism of many important psychotropic agents. Drug interactions involving these enzymes can impact on plasma concentrations, leading either to excess side effects and toxicity or, conversely, to reduced efficacy and duration of action of administered drugs. Awareness of the cytochrome P450 enzyme system is essential to safe and rational prescribing.
- Genetic polymorphisms in expression of metabolizing enzymes cause certain individuals to experience intolerable side effects at standard doses of common psychotropic drugs. The possibility that individuals intolerant of multiple drugs may be 'poor metabolizers' must be considered.
- Pharmacokinetic interactions are also of great clinical relevance to the renally excreted drug lithium, especially as this compound has a narrow therapeutic window, meaning that small changes in its excretion can cause toxic effects.
- The impact of medical illness and advancing age on drug handling, and therefore on plasma concentration and clinical effect, must be taken into account.

## Absorption

Absorption is the entry of a drug into the body. Psychotropic drugs are most commonly prescribed for oral administration and are absorbed mainly through the wall of the small bowel, but they may also be given intramuscularly (i.m.) and occasionally by direct intravenous (i.v) injection.

When a drug is taken orally it is absorbed into the blood supply that passes through the liver (the hepatic venous supply). This means that the liver can act on the drug before it reaches other sites, especially the brain. Often the liver metabolizes a significant proportion of a drug before it can enter the rest of the circulation – the 'first-pass' effect. In patients with liver disease, first-pass metabolism is frequently reduced, which can lead to higher plasma concentrations than anticipated and potential toxicity.

The rate of absorption can be an important factor in the efficacy and utility of a drug. Intramuscular administration of psychotropic agents avoids first-pass metabolism and allows compounds to act on their intended target (the brain) more rapidly, which may be an important consideration in emergency situations such as acute behavioural disturbance in psychosis. In contrast, intramuscular 'depot' preparations are used for antipsychotic drugs (e.g. haloperidol, zuclopenthixol and risperidone) to allow patients requiring long-term treatment to receive the drug at intervals of 2–4 weeks. The active drug is released gradually from an oily vector over the interim period for absorption. Similarly, 'extended-release' oral preparations (such the form of venlafaxine marketed in the UK as *Efexor XL*) allow compounds which otherwise must be taken 2 or 3 times daily, to be prescribed as a

more manageable once-daily preparation. The absorption period is prolonged because the active compound is contained within spheroids and diffuses gradually across a coating membrane.

Another aspect of drug absorption of clinical relevance relates to drug misuse. The rapid rise in blood levels seen after intravenous injection, both of illicit drugs and also of benzodiazepines such as temazepam, can induce a pleasurable 'rush', leading to abuse.

## Distribution

Distribution is the spread of a drug through the body. Several factors determine which tissues a drug can access. Drugs that are very water-soluble (hydrophilic) tend to be concentrated in blood plasma, whereas more fat-soluble (lipophilic) drugs concentrate in fat stores and fatty organs such as the brain. In addition, the blood–brain barrier is more permeable to small lipophilic molecules. Hence diazepam enters the brain more readily than lorazepam, which is less lipophilic. The possibility that electroconvulsive therapy (ECT) can increase blood–brain barrier permeability, allowing drugs normally remaining in the plasma to enter the brain, should always be considered when arranging this form of treatment.

There are two distinct distribution phases: primary, referring to the initial time course of drug disposition, and secondary, referring to the redistribution phase (Figure 1), in which the drug moves into different body compartments. This phenomenon is well illustrated by diazepam, which, after an initial primary distribution phase into blood and brain, then enters a secondary redistribution phase into body fat stores. Brain levels may therefore fall from those seen in the primary phase.

## Drug metabolism and excretion

Psychotropic drugs are removed from the body by two processes: metabolism, which occurs mainly in the liver, and excretion, the elimination of the drug from the body, which may be from the liver into bile and then the gut, or from the kidney. Lithium carbonate and the antipsychotic amisulpride, being highly water- soluble, are rare examples of psychotropic drugs excreted unchanged by the kidneys. Lorazepam excretion is mostly via the kidney, which makes it the benzodiazepine of choice in patients with liver impairment.

However, most psychotropic agents need to be converted to metabolites with more polar structures to facilitate excretion via the liver or kidney. Metabolism consists of two distinct phases: phase I involving oxidation, reduction or hydrolysis in the liver, and phase II conjugation, commonly with sulphate or glucuronic acid in the liver or gut wall.

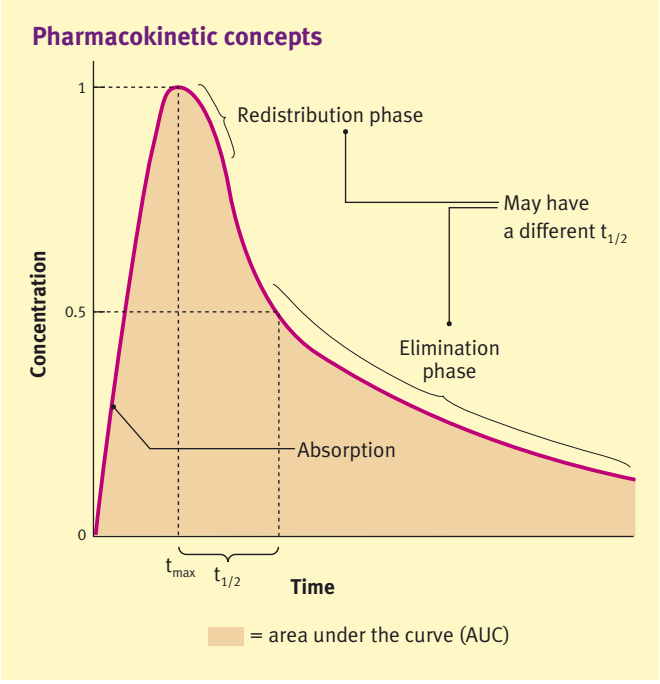


**Figure 1**

### Liver metabolism

Some drugs are metabolized in phase I to other known psychotropic agents (e.g. amitriptyline to nortriptyline, clomipramine to imipramine, lofepramine to desipramine), while others have active metabolites which, although not prescribed in their own right, contribute to the therapeutic effect (e.g. nor-fluoxetine, o-desmethyl venlafaxine). Some compounds, such as the benzodiazepine clorazepate and the analgaesic agent tramadol, require liver metabolism in order to be effective, as the metabolite is the active compound, rather than the administered drug, which is referred to as a 'pro-drug'.

**Cytochrome P450 enzymes:** phase I metabolism, which is effected by a series of hepatic enzymes known as cytochrome P450 (CYP) isozymes, is of considerable clinical relevance in psychotropic drug use.[1,2] Drugs may be substrates, inhibitors or inducers of one or more P450 enzymes. Introducing or stopping a drug which is metabolized by, or otherwise influences the activity of, a particular enzyme, may have ramifications for the plasma concentrations of existing drugs. Additionally, existing drugs may influence the eventual concentration of a newly introduced drug, with implications for efficacy, adverse effects and toxicity.

***Substrates*** – a *substrate* is something that is changed by an enzyme. Many antidepressants, anxiolytics, hypnotics and antipsychotics are substrates of CYP2D6 (Table 1) and CYP3A4 (Table 2). Other CYP enzymes metabolize psychotropic agents, notably CYP1A2 (olanzapine, clozapine) and CYP2C19 (involved in the metabolism of various anxiolytics and antidepressants including amitriptyline, moclobemide and diazepam). Some drugs can be substrates for several CYP enzymes; for example, the desmethylation of sertraline to its metabolite can be effected by six different CYP enzymes.

***Inhibitors*** – an *inhibitor* interferes with the ability of an enzyme to effect metabolism, retarding the breakdown of co-prescribed drugs and thus potentially increasing their plasma levels. Paroxetine and fluoxetine are relatively strong inhibitors of CYP2D6.[3] Duloxetine may also act as a moderately potent CYP2D6 inhibitor.[4] Fluoxetine also inhibits CYP3A4 and fluvoxamine inhibits CYP1A2. CYP2D6 inhibitors increase zuclopenthixol concentrations, which may have clinical relevance in the dose selection of zuclopenthixol actetate in rapid tranquillization situations when the subject is already taking fluoxetine or paroxetine. CYP2D6 inhibition effected by these selective serotonin reuptake inhibitors (SSRIs) on thioridazine can increase this antipsychotic's plasma concentration and enhance the risk of QTc prolongation and cardiac arrhythmia; these combinations are therefore contraindicated.

## Psychotropic (and selected other) drugs known to be CYP2D6 substrates, inhibitors and inducers

**CYP2D6 inhibitors**

*Antidepressants*
Paroxetine
Fluoxetine
Duloxetine

**CYP2D6 substrates**

| *Antidepressants* | *Antipsychotics* | *Miscellaneous* |
|---|---|---|
| Paroxetine | Aripiprazole | Buproprion |
| Fluoxetine | Chlorpromazine | β-blockers |
| Citalopram | Haloperidol | Propanolol |
| Sertraline | Thioridazine | Metoprolol |
| Venlafaxine | Zuclopenthixol | Timolol |
| Amitriptyline | Perphenazine | Bufaralol |
| Clomipramine | Risperidone | Dexfenfluramine |
| Desipramine | | Ecstasy |
| Imipramine | | Opioids |
| Nortriptyline | | Codeine |
| | | Hydrocodone |
| | | Dihydrocodeine |
| | | Tramadolol |
| | | Ethyl morphine |

**Table 1**

## Psychotropic (and selected other) drugs known to be CYP3A4 substrates, inhibitors and inducers

**CYP3A4 inhibitors**

| *Antidepressants* | *Other drugs* |
|---|---|
| Nefazodone | Cimetidine |
| Fluoxetine | Erythromycin |
| | Ketoconazole (and grapefruit Juice) |

**CYP3A4 substrates**

| *Antidepressants* | *Anxiolytics, hypnotics and antipsychotics* | *Miscellaneous* |
|---|---|---|
| Fluoxetine | Alprazolam | Buprenorphine |
| Sertraline | Aripiprazole | Carbamazepine |
| Amitriptyline | Buspirone | Cortisol |
| Imipramine | Diazepam | Dexamethasone |
| Nortriptyline | Midazolam | Methodone |
| Trazodone | Triazolam | Testosterone |
| | Zoplicone | Calcium channel blockers |
| | Haloperidol | Diltiazem |
| | Quetiapine | Nifedipine |
| | Sertindole | Amlodipine |
| | | Other drugs |
| | | Amiodarone |
| | | Omeprazole |
| | | Oral contraceptives |
| | | Simvastatin |

**CYP3A4 inducers**

| *Antidepressants* | *Miscellaneous* |
|---|---|
| St John's wort | Carbamazepine |
| | Phenobarbitone |
| | Phenytoin |

**Table 2**

When several substrates of the same enzyme are prescribed together (e.g. nortriptyline + codeine + metoprolol), the metabolism of one or more drugs may also be inhibited, resulting in elevated plasma concentrations and possibly increased side effects. Plasma concentrations of some substrate drugs, such as aripiprazole, can be raised both by inhibitors of CYP2D6 and by CYP3A4 inhibitors.

***Inducers*** – an *inducer* speeds up enzyme activity, usually by causing the synthesis of greater amounts of enzyme, such that any co-prescibed drug metabolized by the same CYP enzyme will be broken down more rapidly. Carbamazepine, an antiepiletic drug with mood-stabilizing properties, is sometimes prescribed with antipsychotic agents when treating bipolar affective disorder. Clinicians must be aware that as a CYP3A4 inducer, carbamazapine can cause plasma concentration, and therefore the clinical effect, of existing antipsychotics to be reduced. In epilepsy, a common comorbid condition in patients with learning disabilities who have psychiatric illness, the combination of CYP3A4-inducing antiepileptic agents (carbamazepine, phenytoin) with CYP3A4-inhibiting SSRI antidepressants (fluoxetine, nefazodone) may make plasma concentrations of both drugs, and therefore epileptic control, difficult to predict, especially as SSRIs can reduce seizure threshold. Care should be taken in starting CYP3A4 inducers for patients taking oral contraceptive drugs which are CYP3A4 substrates – for example, the popular herbal remedy St John's wort has CYP3A4-inducing effects and may therefore compromise contraceptive efficacy. Cigarette smoking can cause CYP1A2 induction and may therefore reduce plasma levels of clozapine, which may overshoot if smoking stops.[5]

**Genetic variations in metabolizer status:**[6] a further point to note when considering CYP2D6 interactions is that 7% of the Caucasian population lack this important enzyme and are referred to as poor metabolizers. Such individuals may find standard tricyclic antidepressant doses intolerable but respond well to very low doses. In some centres these poor metabolizers can be identified by blood sampling for genotyping, otherwise they may be characterized by their response to a test drug such as debrisoquine. In contrast, 'extensive metabolizer' status has been reported in up to 29% of a North African population. These individuals, who are also fairly common in populations of Middle Eastern origin, have abundant CYP2D6 enzyme availability. They may require significantly higher doses of substrate drugs to produce a similar clinical effect as that seen in the majority of the population who are referred to as 'intermediate metabolizers'. CYP2C19 also has a genetic polymorphism of clinical significance, with the frequency of poor metabolizers among East Asians being up to 25%.

Another genetic polymorphism of relevance when prescribing the monoamine oxidase inhibitor (MAOI) phenelzine relates to the phase II conjugation process of acetylation. As a result of this

polymorphism, individuals may be fast or slow acetylators, with consequences for phenelzine plasma concentration and clinical effect.

### Renal excretion

Lithium is eliminated only by the kidneys. Like sodium, it is filtered by the glomerulus and 80% is reabsorbed by the proximal tubule, but it is not reabsorbed by the distal tubule. The intake of sodium and water are the principal determinants of its elimination. Any reduction in the rate of clearance of lithium can have profound clinical implications, since the range of plasma concentrations for therapeutic effect is relatively small but concentrations slightly higher are associated with toxicity; thus it has a narrow therapeutic window. Reduced renal function or co-prescription of diuretics, especially thiazides, which induce sodium deficiency, can reduce lithium excretion significantly and thus precipitate toxicity. ACE inhibitors, angiotensin-II-antagonists, and non-steroidal anti-inflammatory analgesics may also raise plasma lithium by interfering with excretion.

## Further key concepts

### Half-life (half-time, $t_{1/2}$)

Half-life is a measure of the longevity of a drug in a tissue (e.g. plasma or brain), and is defined as the time taken for its concentration to fall by half (Figure 1).

In addition to co-administration of other medications which interfere with metabolism, half-life is influenced by co-existent medical conditions (especially liver disease) and age (as the elderly tend to metabolize drugs more slowly – see below). For some drugs, brain half-life can now be measured using positron emission tomography (PET) and single photon emission computed tomography (SPECT), both of which are imaging techniques that detect gamma rays produced after decay of radiolabelled compounds.

### Steady state

This describes the condition when the concentration of a drug has become stable (Figure 2). It occurs when the rate of entry of a drug into plasma equals that of its clearance. The time taken to reach steady state is determined by two factors: drug half-life and the dosing schedule. If a drug is administered at an interval equal to its half-life then it takes 4–5 doses to reach steady state. For example, lorazepam (half-life 17 hours) taken once daily will attain steady state in up to 4 days. Diazepam takes longer because its half-life is 30 hours, but there is further complexity in that the time to obtain steady state for all active benzodiazepines is much greater because of the very long half-life of the main metabolite desmethyldiazepam (100 hrs).

### Linear vs non-linear kinetics

The majority of psychotropic agents exhibit linear, or first-order, kinetics, whereby the steady state plasma concentration can be predicted linearly from the dose. However, non-linear kinetics applies to drugs where the main metabolizing enzyme becomes saturated within the normal dose range. Clinically relevant examples of psychotropic drugs with non-linear kinetics are fluoxetine and paroxetine, since they inhibit CYP2D6, the same CYP enzyme that is the major route for their metabolism. As these SSRIs reach steady state, plasma concentrations depart from the linear relation with dose since their inhibition of the CYP2D6 enzyme retards their own breakdown. For some drugs there appears to be virtually no relationship between dose and plasma concentration, the classic example being the anti-epileptic agent phenytoin, which is said to have 'zero-order' kinetics. A study of 200 patients given the same dose of phenytoin reported a 50-fold difference in plasma concentration assayed at a fixed time after dosing. For such drugs, plasma concentration monitoring is essential to safe prescribing.

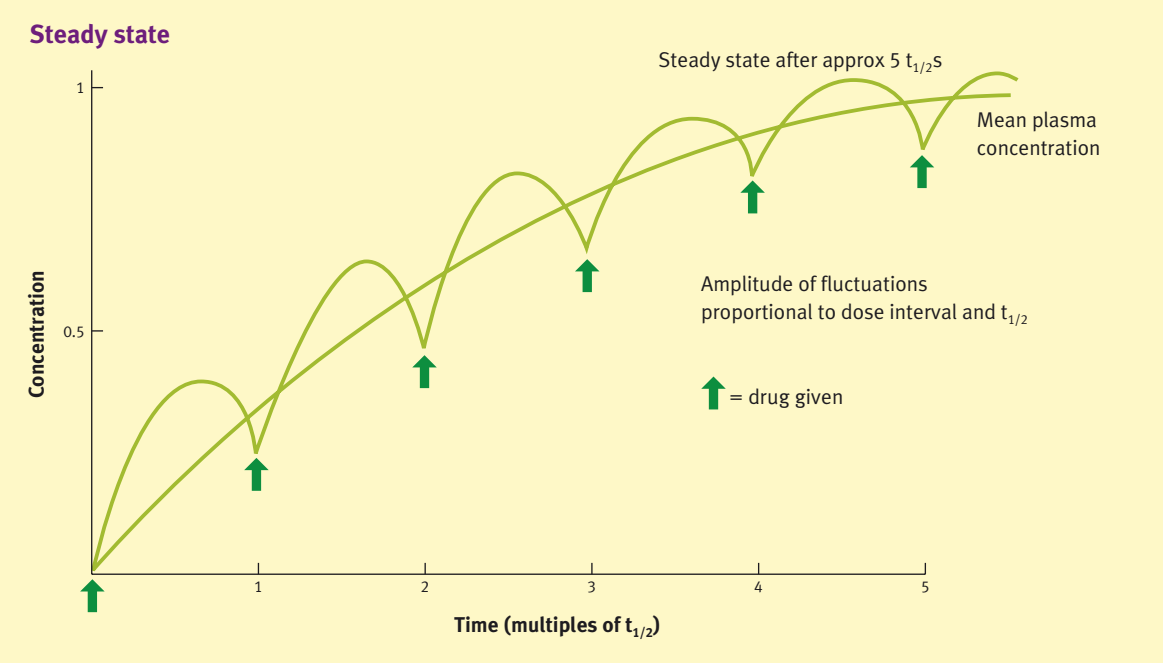


**Figure 2**

### Area under the curve

Area under the curve (AUC) represents the total amount of drug present in the body over time (Figure 1). It is influenced by the rate at which the drug is metabolized and excreted. Thus in individuals where metabolism occurs more slowly than in the general population, such as the elderly and poor metabolizers with respect to CYP2D6, AUC is increased.

### Bioavailability

Biovailability is the fraction of an orally administered drug which reaches systemic blood without being metabolized. Clearly drugs with a high first-pass metabolism tend to have low bioavailability. Since the portal system and therefore first-pass metabolism is avoided by intravenous administration, bioavailability may also be calculated by [AUC for oral administration] divided by [AUC for i.v. administration of the same dose].

### Pharmacokinetic changes in the elderly

Changes in drug handling commonly occur with advancing age. Reduced acid production in the stomach and diminished blood flow can lead to reduced rates of drug absorption. Alterations in body composition, such as reduction in total body weight, relative increase in fat composition and reduction in availability of albumin, may modify drug distribution. Changes in hepatic activity can alter the relative importance of metabolic pathways, while for renal excretion the glomerular filtration rate and therefore clearance decreases progressively with age. One study of the benzodiazepine triazolam compared plasma concentration and clinical effect between young and old and reported that the two were closely linked. However, plasma concentration was significantly higher in the elderly group, underlining the need for reduced doses in older patients and suggesting that pharmacokinetic change, not receptor sensitivity, is the key distinguishing factor between the age groups.

## Summary

For the many reasons outlined in this contribution, an understanding of the principles of pharmacokinetics is important in rational drug prescribing. A knowledge of pharmacokinetics is of particular relevance in individuals whose ability to metabolize prescribed medication may be altered through co-prescribed drugs and polypharmacy, concomitant use of other substances, physical health problems or changes associated with age. ◆


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## FURTHER READING

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(*Another excellent general text, with dedicated chapters on drug interactions, pharmacogenetics and drug handling in the elderly.*)

## Practice points

- The therapeutic action of drugs may be prolonged by modifying rate of absorption, as is the case with extended-release and depot preparations. In addition, many drugs, including diazepam, fluoxetine and venlafaxine, have active metabolites that remain in plasma considerably longer than the parent compound, extending the therapeutic effect
- Prescribers should be familiar with substrates, inhibitors and inducers of the most important hepatic cytochrome P450 enzymes. For example:
  - inhibition of CYP2D6 by paroxetine or fluoxetine can raise plasma concentration and cardiovascular risk attributable to thioridazine
  - carbamazepine and St John's wort induce CYP3A4, causing reduced plasma concentration of several important psychotropic agents and the oral contraceptive pill
  - cigarette smoking may induce CYP1A2, leading to reduced concentrations of clozapine
- Genetically determined poor metabolizers with respect to the CYP2D6 enzyme may experience repeated intolerance to antidepressant drugs, but may tolerate reduced doses
- Since lithium has a narrow therapeutic window above which toxic effects are likely, prescribers must be aware of drugs interfering with its renal excretion