Plasma drug concentration or plasma ‘level’ monitoring is a process surrounded by some confusion and misunderstanding. Drug level monitoring, when appropriately used, is of considerable help in optimising treatment and assuring adherence. However, in psychiatry, as in other areas of medicine, plasma level determinations are frequently undertaken without good cause and results acted upon inappropriately. Conversely, in other instances, plasma levels are underused.

Before taking a blood sample for plasma level assay, make sure that the following criteria are satisfied.

- **Is there a clinically useful assay method available?** Only a minority of drugs have available assays. The assay must be clinically validated and results available within a clinically useful timescale. Check with your local laboratory.
- **Is the drug at ‘steady state’?** Plasma levels are usually meaningful only when samples are taken after steady-state levels have been achieved. This takes 4–5 drug half-lives. A clear exception to this advice is suspected overdose; in such situations attainment of steady state is of no relevance.
- **Is the timing of the sample correct?** Sampling time is vitally important for many but not all drugs. If the recommended sampling time is, say, 12 hours post dose, then the sample should be taken 11–13 hours post dose if possible; 10–14 hours post dose, if absolutely necessary. For trough or ‘pre-dose’ samples, take the blood sample immediately before the next dose is due. Do not, under any circumstances, withhold the next dose for more than 1 or (possibly) 2 hours until a sample is taken. Withholding for longer than this will inevitably give a misleading result (it will give a lower result than that ever seen in the usual, regular dosing), and this may lead to an inappropriate dose increase. Sampling time is less critical with drugs with a long half-life (e.g. olanzapine) but, as an absolute minimum, prescribers should always record the time of sampling and time of last dose. This cannot be emphasised enough.
If a sample is not taken within 1–2 hours of the required time, it has the potential to mislead rather than inform. The only exception to this is if toxicity is suspected – sampling at the time of suspected toxicity is obviously appropriate.

**Will the level have any inherent meaning?** Is there a target range of plasma levels? If so, then plasma levels (from samples taken at the right time) will usefully guide dosing. If there is not an accepted target range, plasma levels can only indicate adherence or potential toxicity. However, if the sample is being used to check compliance, then bear in mind that a plasma level of zero indicates only that the drug has not been taken in the past several days. Plasma levels above zero may indicate erratic compliance, full compliance or even long-standing non-compliance disguised by recent taking of prescribed doses. Note also that target ranges have their limitations: patients may respond to lower levels than the quoted range and tolerate levels above the range; also, ranges quoted by different laboratories vary sometimes widely, often without explanation.

**Is there a clear reason for plasma level determination?** Only the following reasons are valid:
- to confirm compliance (but see above)
- if toxicity is suspected
- if drug interaction is suspected
- if clinical response is difficult to assess directly (and where a target range of plasma levels has been established)
- if the drug has a narrow therapeutic index and toxicity concerns are considerable.

### Interpreting sample results

The basic rule for sample level interpretation is to act upon assay results only in conjunction with reliable clinical observation (‘treat the patient, not the level’). For example, if a patient is responding adequately to a drug but has a plasma level below the accepted target range, then the dose should not normally be increased. If a patient has intolerable adverse effects but a plasma level within the target range, then a dose decrease may be appropriate.

Where a plasma level result is substantially different from previous results, a repeat sample is usually advised. Check dose, timing of dose and recent compliance but ensure, in particular, the correct timing of the sample. Many anomalous results are the consequence of changes in sample timing.

Table 1.1 shows the target ranges for some commonly prescribed psychotropic drugs.

### Amisulpride

Amisulpride plasma levels are closely related to dose with insufficient variation to make routine plasma level monitoring prudent. Higher levels observed in women\(^{17–19}\) and older age\(^{17,19}\) seem to have little significant clinical implication for either therapeutic response or adverse effects. A (trough) threshold for clinical response has been suggested to be approximately 100 \(\mu g/L\)\(^{20}\) and mean levels of 367 \(\mu g/L\)\(^{19}\) have been noted in responders in individual studies. Adverse effects (notably extrapyramidal side-effects, EPS) have been observed at mean levels of 336 \(\mu g/L\), 377 \(\mu g/L\)\(^{20}\) and 395 \(\mu g/L\).\(^{18}\) A plasma
<table>
<thead>
<tr>
<th>Drug</th>
<th>Target range</th>
<th>Sample timing</th>
<th>Time to steady state</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amisulpride</td>
<td>200–320 µg/L</td>
<td>Trough</td>
<td>3 days</td>
<td>See text</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>150–210 µg/L</td>
<td>Trough</td>
<td>15–16 days</td>
<td>See text</td>
</tr>
<tr>
<td>Carbamazepine^2,3</td>
<td>&gt;7 mg/L bipolar disorder</td>
<td>Trough</td>
<td>2 weeks</td>
<td>Carbamazepine induces its own metabolism. Time to steady state dependent on autoinduction</td>
</tr>
<tr>
<td>Clozapine</td>
<td>350–500 µg/L Upper limit of target range is ill-defined</td>
<td>Trough</td>
<td>2–3 days</td>
<td>See text</td>
</tr>
<tr>
<td>Lamotrigine^4-6</td>
<td>Not established but suggest 2.5–15 mg/L</td>
<td>Trough</td>
<td>5 days</td>
<td>Autoinduction is thought to occur, so time to steady state may be longer</td>
</tr>
<tr>
<td>Lithium^7-11</td>
<td>0.6–1.0 mmol/L (0.4 mmol may be sufficient for some patients/indications; &gt;1.0 mmol/L required for mania)</td>
<td>12 hours post-dose</td>
<td>5 days</td>
<td>Well-established target range, albeit derived from ancient data sources</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>20–40 µg/L</td>
<td>12 hours</td>
<td>1 week</td>
<td>See text</td>
</tr>
<tr>
<td>Paliperidone^12</td>
<td>20–60 µg/L (9-OH risperidone)</td>
<td>Trough</td>
<td>2–3 days oral</td>
<td>No obvious reason to suspect range should be any different from risperidone. Some practical confirmation. As with risperidone, plasma level monitoring is not recommended</td>
</tr>
<tr>
<td>Phenytoin^1</td>
<td>10–20 mg/L</td>
<td>Trough</td>
<td>Variable</td>
<td>Follows zero-order kinetics. Free levels may be useful</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Around 50–100 µg/L?</td>
<td>Trough?</td>
<td>2–3 days oral</td>
<td>Target range not defined. Plasma level monitoring not recommended. See text</td>
</tr>
<tr>
<td>Risperidone</td>
<td>20–60 µg/L (active moiety – risperidone + 9OH risperidone)</td>
<td>Trough</td>
<td>2–3 days oral 6–8 weeks depot</td>
<td>Plasma level monitoring is not recommended. See text</td>
</tr>
<tr>
<td>Tricyclics^13</td>
<td>Nortriptyline 50–150 µg/L Ammitriptyline 100–200 µg/L</td>
<td>Trough</td>
<td>2–3 days</td>
<td>Rarely used and of dubious benefit Use electrocardiogram to assess toxicity</td>
</tr>
<tr>
<td>Valproate^2,3,14-16</td>
<td>50–100 mg/L Epilepsy and bipolar</td>
<td>Trough</td>
<td>2–3 days</td>
<td>Some doubt over value of levels in epilepsy and in bipolar disorder. Some evidence that, in mania, levels up to 125 mg/L are tolerated and more effective than lower concentrations</td>
</tr>
</tbody>
</table>
The plasma level threshold of below 320 μg/L has been found to predict avoidance of EPS. A review of the current literature has suggested an approximate range of 200–320 μg/L for optimal clinical response and avoidance of adverse effects.

In practice, only a minority of treated patients have ‘therapeutic’ plasma levels (probably because of poor adherence) so plasma monitoring may be of some benefit. However, amisulpride plasma level monitoring is rarely undertaken and few laboratories offer amisulpride assays. The dose–response relationship is sufficiently robust (in trials, at least) to obviate the need for plasma sampling within the licensed dose range and adverse effects are well managed by dose adjustment alone. Plasma level monitoring is best reserved for those in whom clinical response is poor, adherence is questioned or in whom drug interactions or physical illness may make adverse effects more likely.

**Aripiprazole**

Plasma level monitoring of aripiprazole is rarely undertaken in practice. The dose–response relationship for aripiprazole is well established with a plateau in clinical response and D₂ dopamine occupancy seen in doses above approximately 10 mg/day. Plasma levels of aripiprazole, its metabolite and the total moiety (parent plus metabolite) strongly relate linearly to dose, making it possible to predict, with some certainty, an approximate plasma level for a given dose. Target plasma level ranges for optimal clinical response have been suggested as 146–254 μg/L and 150–300 μg/L, with adverse effects observed above 210 μg/L. Interindividual variation in aripiprazole plasma levels has been observed but not fully investigated, although gender appears to have little influence. Age, metabolic enzyme genotype and interacting medications seem likely causes of variation but there are too few reports regarding their clinical implication to recommend specific monitoring in respect to these factors. A putative range of between 150 μg/L and 210 μg/L has been suggested as a target for patients taking aripiprazole and these are broadly the concentrations seen in patients receiving depot aripiprazole at 300 mg and 400 mg monthly. However, for reasons described here, plasma level monitoring is not advised in routine practice.

**Clozapine**

Clozapine plasma levels are broadly related to daily dose but there is sufficient variation to make any precise prediction of plasma level impossible. Plasma levels are generally lower in younger patients, males and smokers and higher in Asians. A series of algorithms has been developed for the approximate prediction of clozapine levels according to patient factors and these are strongly recommended. Algorithms cannot, however, account for other influences on clozapine plasma levels such as changes in adherence, inflammation and infection.

The plasma level threshold for acute response to clozapine has been suggested to be 200 μg/L, 350 μg/L, 370 μg/L, 420 μg/L, 504 μg/L and 550 μg/L. Limited data suggest a level of at least 200 μg/L is required to prevent relapse. Substantial variation in clozapine plasma level may also predict relapse.

Despite these somewhat varied estimates of response threshold, plasma levels can be useful in optimising treatment. In those not responding to clozapine, dose should
be adjusted to give plasma levels in the range 350–500 μg/L (a range reflecting a consensus of the above findings). Those not tolerating clozapine may benefit from a reduction to a dose giving plasma levels in this range. An upper limit to the clozapine target range has not been defined. Any upper limit must take into account two components: the level above which no therapeutic advantage is gained and the level at which toxicity/tolerability is unacceptable. Plasma levels do seem to predict electroencephalogram (EEG) changes and seizures occur more frequently in patients with levels above 1000 μg/L so levels should probably be kept well below this. Other non-neurological clozapine-related adverse effects also seem to be related to plasma level, as might be expected. No ‘therapeutic’ upper limit has been defined although levels around 600–800 μg/L have been proposed.

A further consideration is that placing an upper limit on the target range for clozapine levels may discourage potentially worthwhile dose increases within the licensed dose range. Before plasma levels were widely used, clozapine was fairly often given in doses up to 900 mg/day, with valproate being added when the dose reached 600 mg/day. It remains unclear whether using these high doses can benefit patients with plasma levels already above the accepted threshold. Nonetheless, it is prudent to use an anticonvulsant as prophylaxis against seizures and myoclonus when plasma levels are above 600 μg/L (a level based more on repeated recommendation than on a clear evidence-based threshold) and certainly when levels approach 1000 μg/L.

Norclozapine is the major metabolite of clozapine. The ratio of clozapine to norclozapine averages 1.25 in populations but may differ for individuals. In chronic dosing, the ratio should remain the same for a given patient. A decrease in ratio may suggest enzyme induction, while an increase suggests enzyme inhibition, a non-trough sample or recent missed doses. Note also that clozapine metabolism may become saturated at higher doses: the ratio of clozapine to norclozapine increases with increasing plasma levels, suggesting saturation. The effect of fluvoxamine also suggests that metabolism via CYP1A2 to norclozapine can be overwhelmed.

Olanzapine

Plasma levels of olanzapine are linearly related to daily dose but there is substantial variation, with higher levels seen in women, non-smokers and those on enzyme-inhibiting drugs. With once-daily dosing, the threshold level for response in schizophrenia has been suggested to be 9.3 μg/L (trough sample), 23.2 μg/L (12-hour post-dose sample) and 23 μg/L at a mean of 13.5 hours post dose. There is evidence to suggest that levels greater than around 40 μg/L (12-hour sampling) produce no further therapeutic benefit than lower levels. Severe toxicity is uncommon but may be associated with levels above 100 μg/L, and death is occasionally seen at levels above 160 μg/L (albeit when other drugs or physical factors are relevant). A target range for therapeutic use of 20–40 μg/L (12-hour post-dose sample) has been proposed for schizophrenia; the range for mania is probably similar. Notably, significant weight gain seems most likely to occur in those with plasma levels above 20 μg/L. Constipation, dry mouth and tachycardia also seem to be related to plasma level.
In practice, the dose of olanzapine should be largely governed by response and tolerability. However, a survey of UK sample assay results suggested that around 20% of patients on 20 mg a day will have sub-therapeutic plasma levels and more than 40% have levels above 40 μg/L. Plasma level determinations might then be useful for those suspected of non-adherence, those showing poor tolerability or those not responding to the maximum licensed dose. Where there is poor response and plasma levels are below 20 μg/L, dose may then be adjusted to give 12-hour plasma levels of 20–40 μg/L; where there is good response and poor tolerability, the dose should be tentatively reduced to give plasma levels below 40 μg/L.

**Quetiapine (IR)**

Dose of quetiapine is weakly related to trough plasma samples. Mean levels reported within the dose range 150 mg/day to 800 mg/day range from 27 μg/L to 387 μg/L, although the highest and lowest levels are not necessarily found at the lowest and highest doses. Age, gender and co-medication may contribute to the significant interindividual variance observed in therapeutic drug monitoring (TDM) studies, with female gender, older age, and CYP3A4-inhibiting drugs likely to increase quetiapine concentration. Reports of these effects are conflicting and not sufficient to support the routine use of plasma level monitoring based on these factors alone. Despite the substantial variation in plasma levels at each dose, there is insufficient evidence to suggest a target therapeutic range to aim for (although a target range of 100–500 μg/L has been proposed); thus plasma level monitoring is likely to have little value. Moreover, the metabolites of quetiapine have major therapeutic effects and their concentrations are only loosely associated with parent drug levels.

Most current reports of quetiapine concentration associations are derived from analysis of trough samples. Because of the short half-life of quetiapine, trough levels tend to drop to within a relatively small range regardless of dose and previous peak level. Thus peak plasma levels may be more closely related to dose and clinical response although monitoring of such is not currently justified in the absence of an established peak plasma target range.

Quetiapine has an established dose–response relationship, and appears to be well tolerated at doses well beyond the licensed dose range. In practice, dose adjustment should be based on patient response and tolerability.

**Risperidone**

Risperidone plasma levels are rarely measured in the UK and very few laboratories have developed assay methods for its determination. In any case, plasma level monitoring is probably unproductive (dose–response is well described) except where compliance is in doubt and in such cases measurement of prolactin will give some idea of compliance.

The therapeutic range for risperidone is generally agreed to be 20–60 μg/L of the active moiety (risperidone + 9-OH-risperidone) although other ranges (25–150 μg/L.
Plasma levels of 20–60 µg/L are usually afforded by oral doses of between 3 mg and 6 mg a day. Occupancy of striatal dopamine D2 receptors has been shown to be around 65% (the minimum required for therapeutic effect) at plasma levels of approximately 20 µg/L.

Risperidone long-acting injection (RLAI) (25 mg/2 weeks) appears to afford plasma levels averaging between 4.4 and 22.7 µg/L. Dopamine D2 occupancies at this dose have been variously estimated at between 25% and 71%. There is considerable interindividual variation around these mean values with a substantial minority of patients with plasma levels above those shown. Nonetheless, these data do cast doubt on the efficacy of a dose of 25 mg/2 weeks although it is noteworthy that there is some evidence that long-acting antipsychotic preparations are effective despite apparently sub-therapeutic plasma levels and dopamine occupancies. Perhaps more importantly, a report of assay results for patients receiving RLAI found 50% of patients with levels below 20 µg/L and for 10% no risperidone/9-hydroxyrisperidone was detected. Thus therapeutic drug monitoring might be clinically helpful for those on RLAI but this rather defeats the object of a long-acting injection.

Limited data for paliperidone palmitate suggest that standard loading doses give plasma levels of 25–45 µg/L while at steady state, plasma levels ranged from 10–25 µg/L for 100 mg/month and 15–35 µg/L for 150 mg/month.

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47. Xiang YQ et al. Serum concentrations of clozapine and norclozapine in the prediction of relapse of patients with schizophrenia. Schizophr Res 2006; 83:201–210.


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### Acting on clozapine plasma concentration results

In most developed countries, clozapine plasma concentration monitoring is widely employed. Table 1.2 gives some general advice about actions that should be taken when clozapine levels fall within a certain range. The ranges shown are somewhat arbitrary and convenient – the concentration at which a particular patient might respond cannot be known without a trial of clozapine. Most adverse effects are linearly related to dose or plasma level. That is, there is no step-change in risk of seizures, for example, at a particular dose or plasma concentration.\(^1\) As a consequence, Table 1.2 should be considered more an aid to decision making rather than a rigorous, unbending evidence-based instruction. Note also the effect of tolerance to adverse effects – many patients have a significant adverse effect burden before therapeutic levels are reached.\(^2\)

<table>
<thead>
<tr>
<th>Plasma concentration</th>
<th>Response status</th>
<th>Tolerability status</th>
<th>Suggest action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;350 µg/L</td>
<td>Poor</td>
<td>Poor</td>
<td>Increase dose very slowly to give level of 350 µg/L</td>
</tr>
<tr>
<td></td>
<td>Poor</td>
<td>Good</td>
<td>Increase dose to give level of 350 µg/L</td>
</tr>
<tr>
<td></td>
<td>Good</td>
<td>Poor</td>
<td>Maintain dose. Consider dose reduction if tolerability does not improve</td>
</tr>
<tr>
<td></td>
<td>Good</td>
<td>Good</td>
<td>Continue to monitor. No action required</td>
</tr>
<tr>
<td>350–500 µg/L</td>
<td>Poor</td>
<td>Poor</td>
<td>Increase dose slowly, according to tolerability, to give level of &gt;500 µg/L. Consider prophylactic anticonvulsant.(^1) If no improvement, consider augmentation</td>
</tr>
<tr>
<td></td>
<td>Poor</td>
<td>Good</td>
<td>Increase dose slowly, according to tolerability, to give level of &gt;500 µg/L. Consider prophylactic anticonvulsant.(^1) If no improvement, consider augmentation</td>
</tr>
<tr>
<td></td>
<td>Good</td>
<td>Poor</td>
<td>Maintain dose to see if tolerability improves. Consider dose reduction to give plasma level of around 350 µg/L</td>
</tr>
<tr>
<td></td>
<td>Good</td>
<td>Good</td>
<td>Continue to monitor. No action required</td>
</tr>
<tr>
<td>500–1000 µg/L</td>
<td>Poor</td>
<td>Poor</td>
<td>Consider use of prophylactic anticonvulsant.(^1) Consider augmentation. Attempt dose reduction if augmentation successful</td>
</tr>
<tr>
<td></td>
<td>Poor</td>
<td>Good</td>
<td>Consider use of prophylactic anticonvulsant.(^1) Consider augmentation</td>
</tr>
<tr>
<td></td>
<td>Good</td>
<td>Poor</td>
<td>Attempt slow dose reduction to give plasma level of 350–500 µg/L unless there is known non-response at lower level. If this is the case, maintain dose and consider adding anticonvulsant.(^1) Optimise treatment of adverse effects</td>
</tr>
<tr>
<td></td>
<td>Good</td>
<td>Good</td>
<td>Consider use of prophylactic anticonvulsant.(^1) Maintain dose if good tolerability continues</td>
</tr>
</tbody>
</table>

(Continued)
Table 1.2 (Continued)

<table>
<thead>
<tr>
<th>Plasma concentration</th>
<th>Response status</th>
<th>Tolerability status</th>
<th>Suggest action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1000 µg/L</td>
<td>Poor</td>
<td>Poor</td>
<td>Add anticonvulsant. Attempt augmentation. Reduce dose to give level of &lt;1000 µg/L. Consider abandoning clozapine treatment</td>
</tr>
<tr>
<td></td>
<td>Poor</td>
<td>Good</td>
<td>Add anticonvulsant. Attempt augmentation. If augmentation successful, reduce dose to give level &lt;1000 µg/L. If unsuccessful, consider abandoning clozapine treatment</td>
</tr>
<tr>
<td></td>
<td>Good</td>
<td>Poor</td>
<td>Add anticonvulsant. Attempt dose reduction to give plasma level &lt;1000 µg/L</td>
</tr>
<tr>
<td></td>
<td>Good</td>
<td>Good</td>
<td>Add anticonvulsant. Monitor closely; attempt dose reduction only if tolerability declines</td>
</tr>
</tbody>
</table>

Notes:
- **Poor response**: No response or unsatisfactory response to clozapine. Not sufficiently well to be discharged.
- **Good response**: Obvious positive changes related to use of clozapine. Likely to be suitable for discharge to supported or unsupported care in the community.
- **Poor tolerability**: Dose constrained by adverse effects such as tachycardia, sedation, hypersalivation, hypotension (see Chapter 2 for suggestions of treatment for adverse effects).
- **Good tolerability**: Patient tolerates treatment well and there are no signs of serious toxicity.
- **Augmentation**: Adding another antipsychotic or mood stabiliser (see Chapter 2).

In all situations, ensure adequate treatment for clozapine-induced constipation, which is dose-related. Ensure regular bowel movements and record bowel function. Stimulant laxatives such as senna often required (see Chapter 2).

Seizures are dose- and plasma-level dependent. Suitable anticonvulsants are valproate, lamotrigine and, rarely, topiramate. Use lamotrigine if response poor; valproate if affective symptoms present (see Chapter 2).

*This table applies to results for patients on a stable clozapine dose with confirmed good adherence.
†Anticonvulsants should be used in patients whose plasma level exceeds 600 µg/L, unless electroencephalogram is normal.

References
Interpreting post-mortem blood concentrations

A great many drugs are subject to post-mortem concentration changes but, for obvious practical reasons, research into the mechanisms and extent of these effects is very limited. The best that can be said is that a drug plasma concentration measured during life may be very different from the (usually whole blood) concentration measured some time after death.

A number of processes are responsible for these changes in concentration. In life, active mechanisms serve to concentrate some drugs in certain organs or tissues. After death, passive diffusion occurs as cell membranes break down and this will mean that post-mortem blood samples will, for some drugs, show higher concentrations than were seen during life. (This is known as post-mortem redistribution (PMR) and has been described as a ‘toxicological nightmare’ because of the number of different processes involved.) In addition, central blood vessels surrounding major organs often reveal much higher drug concentrations than relatively distant peripheral samples. PMR and other processes are temperature- and time-dependent and so time since death and conditions of storage are important determinants of blood concentration changes. Post-mortem redistribution tends to be greater with drugs with a large volume of distribution (i.e. those for which tissue concentrations in life vastly exceed blood concentrations), especially when given over a long period during life.

Other processes of importance include the post-mortem synthesis of certain compounds. The body can generate γ-hydroxybutyrate and trauma may allow the introduction of yeasts that metabolise glucose to alcohol. Another phenomenon is the

| Table 1.3 Factors affecting post-mortem blood concentrations |
|---|---|---|
| Factor | Examples | Consequences |
| Redistribution of drug from tissues to blood compartment | Most drugs with large volume of distribution, e.g. clozapine, olanzapine, methadone, SSRIs, TCAs, mirtazapine | Post-mortem levels up to 10x higher than in-life levels, sometimes higher |
| Uneven distribution of drugs in the blood compartment and in organs (i.e. site of blood collection affects concentration) | Most drugs, e.g. clozapine, TCAs, SSRIs, benzodiazepines | Concentrations may vary several-fold according to site of collection at post-mortem, e.g. femoral blood versus heart blood |
| Decay of drugs in post-mortem tissue (usually by bacterial degradation) | Not widely studied but known to occur with olanzapine, risperidone and some benzodiazepines | Post-mortem levels may be lower than in-life levels |
| Post-mortem metabolism/degradation | Cocaine metabolised/degraded post-mortem. Many other drugs are unstable in post-mortem samples. Yeasts may produce ethanol following trauma | Post-mortem levels may be lower (cocaine) or higher (alcohol) than in-life levels |

SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.
degradation of drugs by bacteria (e.g. clonazepam and nitrazepam). Also, the metabolism of some drugs (cocaine, for example) appears to continue after death (although this may be simple chemical instability of the parent compound).

Table 1.3 lists some of the factors relevant to drug concentration changes after death and the possible consequences of these processes. Generally speaking, an isolated post-mortem blood concentration cannot be sensibly interpreted. Even where in-life levels are available, experts agree that, for most drugs in most circumstances, interpretation of blood levels after death is near impossible: high concentrations should certainly not be taken, in the absence of other evidence, to indicate death by overdose. Expert advice should always be sought when considering the role of medication in a death.5

References