16 - Chapter 11 Pharmacokinetics

01 - Plasma level monitoring of psychotropic drugs

Plasma level monitoring of psychotropic drugs

02 - First order pharmacokinetics

First-order pharmacokinetics

03 - Steady state

Steady state

The Maudsley® Prescribing Guidelines in Psychiatry, Fifteenth Edition. David M. Taylor, Thomas R. E. Barnes and Allan H. Young. © 2025 David M. Taylor. Published 2025 by John Wiley & Sons Ltd. Chapter 11 Plasma level monitoring of psychotropic drugs The measurement of blood or plasma drug concentrations is widely known as therapeutic drug monitoring or TDM. It is often used in psychiatry but not always well used. The interpretation of drug concentrations (drug ‘levels’) is a complex process that requires a thorough understanding of pharmacokinetics. Some principles are outlined here. First-order pharmacokinetics The metabolism and excretion of most drugs follow first-order elimination kinetics. The key feature of this model is that clearance of a drug is constant when expressed in volume per unit time – usually L/h. The mass of drug cleared (metabolised or excreted) increases as blood concentration increases. For example, if clearance of a drug is 10L/h and the concentration is 5mg/L then 50mg (10×50mg) will be cleared in an hour. If the concentration increases to 10mg/L then 100mg will be cleared in an hour. The concept of first--order pharmacokinetics is important to the understanding of steady state. Steady state Repeated dosing of any drug that is not completely removed within the dosing interval will inevitably lead to accumulation. That is, the second dose will add to what remains of the first and the third dose will add to what remains of the first and second doses. As the drug concentration in the blood increases, the mass of the drug cleared will also rise, according to first-order principles. Eventually, a point is reached where blood levels remain stable within a specific peak-to-trough range – this is steady state. It is important Pharmacokinetics

04 - Timing of sampling

Timing of sampling

866 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 11 to know when a drug is or is not at steady state but there are two concepts connected to steady state that are often misunderstood. ■ ■Time to reach steady state follows a logarithmic pattern The time taken to reach steady state is dependent on the drug half-life – the time taken for concentration to fall by 50%. This table shows the rise to steady state. Number of half-lives % of steady state reached 75% 87.5% 94% 97% Most people know the adage that it takes four to five half-lives to reach steady state. In fact, three half-lives are sufficient for an approximation of steady state concentrations. ■ ■Steady state is not always related to therapeutic activity Blood levels at steady state are determined by dose and drug half-life. The concentration at which therapeutic activity occurs is fixed (see later) and, during therapeutic dosing, is often exceeded before steady state is reached. Loading doses are sometimes used to achieve therapeutic concentrations as quickly as possible. Loading doses do not hasten the achievement of steady state levels. Timing of sampling 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. A study of clozapine samples taken 1 and 2 hours before and after the 12-hour scheduled sample time showed a mean variation of clozapine blood concentration of less than 10%, but some individuals' levels varied by over 50%.1 So, if a sample is not taken within 1–2 hours of the required time, it has the potential to mislead rather than inform. Always try to take samples as close to the scheduled time as possible. Obviously, if toxicity is suspected, take a sample straightaway, ignoring any scheduled timings. 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 the 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, aripiprazole) but, as an absolute minimum, prescribers should always record the time of sampling and time of last dose. This cannot be emphasised enough, and is worth repeating in bold. Always record the time of sampling and the time of the last dose.

05 - Interpretation of results

Interpretation ofÂ results

06 - Target ranges

Target ranges

Pharmacokinetics CHAPTER 11 Interpretation of results 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. This is discussed further later. 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 the dose, the timing of dose and recent compliance but ensure, in particular, the correct timing of the sample, or at the very least that the timing of sampling is known. Many anomalous results are the consequence of changes in sample timing. Target ranges In psychiatry, target ranges for psychotropic drug concentrations should be treated with some caution. Establishing a range of concentrations associated with response is made difficult by the presence in trials of non-responders (who show no response whatever the blood concentration) and by the presence of placebo responders and spontaneous remitters (who respond at any blood concentration). Establishing a target range based on adverse effects is made difficult by the development of tolerance over time. Thus, most studies aimed at determining target ranges have as much ‘noise’ as ‘signal’ and results ultimately represent broad approximations. Interestingly, drug concentrations associated with response in clinical practice show a fairly close correlation to published target ranges.2 The lower quartile (25th percentile) of drug concentrations is usually close to the lower end of the target range and the upper quartile (75th percentile) is around the value of, but usually less than, the upper limit. Broadly speaking, this means that around 25% of patients respond below the target range and up to 25% tolerate blood concentrations above the target range. The simplicity of published target ranges disguises considerable complexity. For most drugs, the concentration at which therapeutic activity appears is fairly constant across a population. This is called the therapeutic threshold – above it, full effect is seen, but below it, activity is lost. A good example here is risperidone where the threshold concentration of active moiety is 20mcg/L. Risperidone and paliperidone could reasonably be considered to have a target concentration rather than a target range of

868 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 11 concentrations. This concept of a therapeutic threshold is supported by neuroimaging studies. A concentration of 20mcg/L of active moiety is associated with a dopamine occupancy of 65–70%3 – the degree of pharmacological activity associated with response for most antipsychotics.4 Increasing dopamine occupancy above this level does not improve efficacy or likelihood of response but does make adverse effects more likely.3 Clozapine is completely different. For clozapine, the target range represents concentrations usually associated with both response and good tolerability. However, perhaps 10% of responders will improve with clozapine concentrations below the target range and as many as 20% of responders will only respond at concentrations above the target range. There is also a so-called point of futility – the concentration above which no additional responders will be uncovered. Responders to clozapine will have blood concentrations between 250 and 1000mcg/L5 – a much wider range than the accepted target range. Unlike risperidone and many other drugs, the threshold concentration is not fixed across populations. This subject is eloquently covered in much more detail in The Clinical Use of Antipsychotic Plasma Levels by Jonathan Meyer and Stephen Stahl (Cambridge University Press, 2021). Table 11.1 discusses the interpretation of sample results for various drugs. Table 11.1 Interpreting sample results for drugs with established target ranges. Drug Target range Sample timing Time to steady state Comments Amisulpride 200–320mcg/L 20–60mcg/L (elderly) Trough 3 days See text Aripiprazole 100–210mcg/L Trough 15–16 days See text Carbamazepine6–8

> 7mg/L Bipolar disorder Trough 2 weeks Carbamazepine induces its own metabolism. Time to steady state dependent on auto-induction Clozapine 350–600mcg/L Trough 2–3 days See text Lamotrigine9–11 Not established but suggest 2.5–15mg/L Trough 5 days Auto-induction is thought to occur, so time to steady state may be longer Some debate over utility of lamotrigine levels, especially in bipolar disorder. In treatment- resistant unipolar depression, plasma levels of above 12.7µmol/L (3.3mg/L) are associated with response.12,13 Toxicity may be increased above 15mg/L but is normally well tolerated Lithium14–18 0.6–1.0mmol/L (0.4mmol may be sufficient for some patients/indications; 1.0mmol/L required for mania) 12 hours 5 days post-dose Well-established target range, albeit derived from ancient data sources. A fairly recent study19 suggested 0.6mmol/L was the minimum level for a prophylactic effect

07 - Amisulpride

Amisulpride

Pharmacokinetics CHAPTER 11 Amisulpride Amisulpride plasma levels are closely related to dose with insufficient variation to make routine plasma level monitoring prudent. Higher levels observed in women27–29 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 100mcg/L30 and mean levels of 367mcg/L29 have been noted in responders. Adverse effects (notably extrapyramidal side effects [EPSEs]) occur at mean levels of 336mcg/L,27 377mcg/L30 and 395mcg/L.28 A plasma level threshold of below 320mcg/L has been found to predict avoidance of EPSEs.30 One review31 has suggested an approximate range of 200–320mcg/L for optimal clinical response and avoidance of adverse effects but a more recent consensus statement32 suggested a target range of 100–320mcg/L. A dose of 200mg a day is sufficient to give a blood level of 100mcg/L33 so this lower threshold is probably too low for a reliable therapeutic effect. In older patients with Drug Target range Sample timing Time to steady state Comments Olanzapine 20–40mcg/L 12 hours 1 week See text Paliperidone20 20–60mcg/L (9-OH risperidone) Trough 2–3 days oral 2 months depot Target range is the same as that established for risperidone.21 As with risperidone, routine plasma level monitoring is not recommended. Phenytoin7 10–20mg/L Trough Variable Follows zero-order kinetics. Free levels may be useful in some circumstances. Quetiapine Around 50–100mcg/L? Trough? 2–3 days oral Target range poorly defined. Plasma level monitoring not recommended. See text. Risperidone 20–60mcg/L (active moiety – risperidone + 9--OH risperidone) Trough 2–3 days oral 6–8 weeks injection Routine plasma level monitoring is not recommended. See text. Tricyclics22 Nortriptyline 50–150mcg/L Amitriptyline 100–200mcg/L Trough 2–3 days Rarely used and of dubious benefit. Use ECG to assess toxicity. Valproate6,7,23–25 50–100mg/L Epilepsy and bipolar Trough 2–3 days Some doubt over value of levels in epilepsy and in bipolar disorder. Some evidence that, in mania, levels up to 125mg/L are tolerated and more effective than lower concentrations. Valproate plasma levels are linearly related to plasma ammonia.26 Table 11.1 (Continued)

08 - Aripiprazole

Aripiprazole

09 - Clozapine

Clozapine

870 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 11 psychosis, studies suggest plasma concentrations of 20–60mcg/L may give optimal D2 occupancy and clinical response.34,35 In practice, only a minority of treated patients have ‘therapeutic’ plasma levels (probably because of poor adherence36) 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 (although in older patients, doses of 50–100mg a day may be sufficient) and adverse effects are usually 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 sometimes 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 10mg/day.37 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.38 Target plasma level ranges for optimal clinical response have been suggested as 146–254mcg/L39 and 150–300mcg/L,40 with adverse effects more frequent above 210mcg/L.40 Inter-individual variation in aripiprazole plasma levels has been observed but not fully investigated, although gender appears to have little influence.41,42 Age, metabolic enzyme genotype and interacting medications seem likely causes of variation.40–43 A putative range of between 150 and 210mcg/L38 has been suggested as a target for patients taking aripiprazole and these are broadly the concentrations seen in patients receiving depot aripiprazole at 300 and 400mg monthly.44 Some authorities suggest a lower threshold for clinical effect of 100mcg/L32 – a plasma level usually afforded by an oral dose of 10mg a day33,45 and around the minimum level reached during treatment with 2-monthly depot.46 Clozapine Clozapine plasma levels are broadly related to daily dose47 but there is sufficient variation to make impossible any precise prediction of plasma level. Plasma levels are generally lower in younger patients, males48 and smokers49 and higher in Asians.50 Much lower doses of clozapine are required in East Asians,51,52 Indians53 and Bangladeshis.54 The prevalence of clozapine poor metabolisers is also higher in East Asians.55,56 A series of algorithms has been developed for the approximate prediction of clozapine levels according to patient factors and these are recommended.57 Dose prediction using genetic analysis is more accurate that algorithm prediction.58 Neither method can account for other influences on clozapine plasma levels such as changes in adherence, inflammation59 and infection.60,61 The plasma level threshold for acute response to clozapine has been suggested to be 200mcg/L,62 350mcg/L,63–65 370mcg/L,66 420mcg/L,67 504mcg/L68 and 550mcg/L.69 Limited data suggest a level of at least 200mcg/L is required to prevent relapse.70 Substantial variation in clozapine

plasma level may also predict relapse.71 Changes in

10 - Olanzapine

Olanzapine

Pharmacokinetics CHAPTER 11 an individual’s clozapine plasma levels are common with a tendency for concentrations to slightly decrease over time,72 although one study suggests a decrease only in norclozapine concentrations.73 Despite these somewhat varied estimates of response threshold, plasma levels can be useful in optimising treatment. In those not responding to clozapine, the dose should be adjusted to give plasma levels in the range 350–600mcg/L (a range reflecting a consensus of the above findings32). 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 EEG changes74,75 and seizures occur more frequently in patients with levels above 1000mcg/L,76 so levels should probably be kept well below this. Other non-neurological clozapine-related adverse effects also seem to be plasma-level related77 as might be expected. An upper limit of concentrations around 600–800mcg/L has been proposed,78 although a level of 1000mcg/L may be the point of futility.79,80 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 sometimes given in doses up to 900mg/day, with valproate being added when the dose reached 600mg/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 antiseizure agent as prophylaxis against seizures and myoclonus when plasma levels are above 600mcg/L (a level based more on repeated recommendation than on being a clear evidence-based threshold78) and certainly when levels approach 1000µmcg/L. Norclozapine is the major metabolite of clozapine. The ratio of clozapine to norclozapine averages 1.25 in populations81 but may differ markedly for individuals.82 In chronic dosing, the ratio should remain the same for a given patient. A decrease in ratio may suggest enzyme induction, an increase suggests enzyme inhibition, a non-trough sample or recent missed doses. Time of sampling radically alters the clozapine/norclozapine ratio as clozapine is relatively high in early samples and norclozapine is higher in late samples.1 Clozapine metabolism may become saturated at higher doses: the ratio of clozapine to norclozapine increases with increasing plasma levels, suggesting saturation.83–85 The effect of fluvoxamine also suggests that metabolism via CYP1A2 to norclozapine can be overwhelmed.86 Ultimately, changes in the clozapine/norclozapine ratio may be impossible to interpret. A systematic review concluded that knowledge of clozapine/norclozapine ratio had no clinical utility.87 Olanzapine Plasma levels of olanzapine are linearly related to daily dose88 but there is substantial variation,89 with higher levels seen in women,68 non-smokers90 and those on enzyme-inhibiting drugs.90,91 With once-daily dosing, the threshold level for response in schizophrenia has been suggested to be 9.3mcg/L (trough sample),92 23.2mcg/L (12-hour post-dose sample)68

and 23mcg/L at a mean of 13.5 hours post-dose.93 There is evidence to suggest that levels greater than around 40mcg/L (12-hour sampling) produce no

11 - Quetiapine

Quetiapine

872 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 11 further therapeutic benefit than lower levels.94 Severe toxicity is uncommon but may be associated with levels above 100mcg/L, and death is occasionally seen at levels above 160mcg/L95 (albeit when other drugs or physical factors are relevant). A target range for therapeutic use of 20–40mcg/L (12-hour post-dose sample) has been proposed96 for schizophrenia; the range for mania is probably similar.97 This target range was for a time widened to 20–80mcg/L98,99 but the reasons for this were not clear. A 2023 systematic review suggests a target range of 20–40mcg/L for 12-hour samples.100 Significant weight gain seems most likely to occur in those with plasma levels above 20mcg/L.101 Constipation, dry mouth and tachycardia also seem to be related to plasma level.102 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 20mg a day will have sub--therapeutic plasma levels and more than 40% have levels above 40mcg/L.103 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 20mcg/L, dose may then be adjusted to give 12-hour plasma levels of 20–40mcg/ L; where there is good response and poor tolerability, the dose should be tentatively reduced to give plasma levels below 40mcg/L. Changes in dose give proportionate changes in plasma levels.104 A case might be made to increase the dose to give blood levels in the range 40–80mcg/L but only where no other options remain. Quetiapine Doses of quetiapine are weakly related to trough plasma samples.105 Mean levels reported within the dose range 150–800mg/day vary from 27 to 387mcg/L,106–111 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 inter- individual variance observed in TDM studies, with female gender,111,112 older age110,111 and CYP3A4-inhibiting drugs106,110,111 likely to increase quetiapine concentration. Reports of these effects are conflicting112 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 100–500mcg/L has been proposed113), 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.114 Most current reports of quetiapine concentration associations are derived from the 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. Peak plasma levels may be more closely related to dose and clinical response,105 although monitoring of such is not currently justified in the absence of an established peak plasma target range. Interestingly, a study of quetiapine in patients with borderline personality disorder or drug-induced psychosis showed a linear relationship between

response and 12-hour plasma levels.112 Peak to trough variation is greater for immediate-release formulations (roughly a maximum of 4000mcg/L to zero) than for slow-release preparations (roughly a maximum of 3000mcg/L to around 100mcg/L).45

12 - Risperidone

Risperidone

13 - Target ranges for other psychotropics

Target ranges for other psychotropics

Pharmacokinetics CHAPTER 11 Quetiapine has an established dose–response relationship, and appears to be well tolerated at doses well beyond the licensed dose range.115 In practice, dose adjustment should be based on patient response and tolerability. Risperidone The therapeutic range for risperidone is generally agreed to be 20–60mcg/L of the active moiety (risperidone + 9--OH-risperidone)98,116,117 although other ranges (25–150mcg/L and 25–80mcg/L) have been proposed.118 Plasma levels of 20–60mcg/L are usually afforded by oral doses of between 3mg and 6mg a day.116,119–121 Occupancy of striatal dopamine D2 receptors has been shown to be around 65% (the minimum required for acute therapeutic effect) at plasma levels of approximately 20mcg/L.117,122 Limited data for paliperidone palmitate 1-monthly long-acting injection (LAI) suggest that standard loading doses give plasma levels of 25–45mcg/L; while at steady state, plasma levels ranged from 10 to 25mcg/L for 100mg/month and 15 to 35mcg/L for 150mg/month.123 Plasma concentrations may gradually rise in the first year of treatment to around 35mcg/L (mean dose 138mg/month)124 and remain stable thereafter.125 For the 3--monthly injection, steady state plasma concentrations range from 30 to 55mcg/L for 525mg every 3 months, 25 to 55mcg/L for 350mg every 3 months and 20 to 35mcg/L for 263mg every 3 months.126,127 Six-monthly paliperidone, available as 700 and 1000mg injections, provides similar plasma concentrations to those achieved by the corresponding doses of 3-monthly injections.128 Plasma concentrations of risperidone ISM® remain above 20mcg/L throughout the dosing interval.129 Target ranges for other psychotropics The target ranges listed in Table 11.2 have somewhat dubious usefulness and, in some cases, merely represent the range of values seen in clinical use. Assays for these drugs are likely to be available only in specialist units. Table 11.2 Target ranges for other psychotropics.32,98,130 Target range (mcg/L) Antipsychotics Asenapine 1–5 Brexpiprazole 40–140 Cariprazine 10–20 Chlorpromazine 30–300 Flupentixol 0.5–5 (cis-isomer) Fluphenazine 1–10 Haloperidol 1–10 (Continued)

874 The Maudsley® Prescribing Guidelines in Psychiatry Table 11.2 (Continued) Iloperidone 5–10 Lurasidone 15–40 Melperone 30–100 CHAPTER 11 Sulpiride 200–1000 Ziprasidone 50–200 Zuclopenthixol 4–50 Antidepressants Agomelatine 7–300 Citalopram 50–110 Desvenlafaxine 100–400 Dosulepin 45–100 Duloxetine 30–120 Escitalopram 15–80 Fluoxetine (+ norfluoxetine)

120–500 Fluvoxamine 60–230 Levomilnacipran 80–120 Mianserin 15–70 Milnacipram 100–150 Mirtazapine 30–80 Moclobemide 300–1000 Paroxetine 20–65 Reboxetine 60–350 Sertraline 10–150 Trazodone 700–1000 Venlafaxine (+ O-desmethylvenlafaxine) 100–400 Vilazodone 30–70 Vortioxetine 15–60 Target range (mcg/L)

14 - References

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15 - Interpreting postmortem blood concentrations

Interpreting postmortem blood concentrations

Pharmacokinetics CHAPTER 11 Interpreting postmortem blood concentrations Much is known about the distribution of drugs in the body during life but relatively little about these same parameters after death. A great many drugs are subject to postmortem distribution 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 concentration measured at some time after death (usually in whole blood from the femoral artery). A number of processes are responsible for these changes. 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 postmortem blood samples will, for some drugs, show higher concentrations than were seen during life. This is known as postmortem redistribution (PMR). In addition, central blood vessels surrounding major organs often demonstrate much higher drug concentrations than relatively distant peripheral samples.1 PMR and other processes are temperature- and time-dependent so time since death and conditions of storage are important determinants of blood concentration changes.2 PMR 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 importance3 include the postmortem synthesis of certain compounds. For example, the body is able to generate gamma-hydroxybutyrate. Trauma may allow the introduction of yeasts that metabolise glucose to alcohol. Another phenomenon is the degradation of drugs by bacteria (e.g. clonazepam and nitrazepam) or fungi. 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). All of the processes described here contribute to an overall direction of change of concentration postmortem. Antidepressant concentrations tend to increase in postmortem samples whereas those of benzodiazepines invariably decrease.4 Mirtazapine concentrations also appear to decrease.5,6 Antipsychotic concentrations both increase and decrease depending on the drug.4

Thus, when an isolated postmortem concentration is considered (i.e. one which cannot be compared with a concentration measured in life), it can only be said that the in-life concentration would have been higher or lower.7 Table 11.3 lists some of the factors relevant to drug concentration changes after death and the possible consequences of these processes. Generally speaking, an isolated postmortem blood concentration cannot be sensibly interpreted. Even where in-life levels are available, for most drugs in most circumstances, interpretation of blood levels after death is near impossible. High postmortem concentrations should certainly not be taken, in the absence of other evidence, to indicate death by overdose, for example. Two valuable reference sources for interpretation of postmortem sample analysis are the systematic reviews of Ketola and Kriikku8 and Ketola and Ojanperä.9 Expert advice should always be sought when considering the role of medication in a death.10

16 - References

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25. Martinez-Ramirez JA, et al. Studies on drug metabolism by fungi colonizing decomposing human cadavers. Part II: biotransformation of five model drugs by fungi isolated from post-mortem material. Drug Test Anal 2015; 7:265–279. Table 11.3 Factors affecting postmortem blood concentrations. Factor Examples Consequences Redistribution of drug from tissues to blood compartment Most drugs with large volume of distribution, e.g. clozapine,11,12 olanzapine,13 methadone,14 SSRIs,15 TCAs, mirtazapine,16 lithium17 May not occur to any significant effect with risperidone,4,18 aripiprazole19 or quetiapine4,19 Postmortem levels up to 10× higher than in-life levels, sometimes higher still9 Uneven distribution of drugs in the blood compartment and in organs (i.e. site of blood collection affects concentration) Most drugs,8,20 e.g. clozapine, TCAs, SSRIs, duloxetine,21 benzodiazepines, quetiapine22 Concentrations may vary several-fold according to site of collection at postmortem, e.g. femoral blood vs heart blood Decay of drugs in postmortem tissue (usually by bacterial degradation) Not widely studied but known to occur with olanzapine, risperidone23 and some benzodiazepines. Fungi can metabolise amitriptyline, mirtazapine and zolpidem.24,25 Postmortem levels may be lower than in-life levels Postmortem metabolism/ degradation Cocaine metabolised/degraded postmortem. Many other drugs are unstable in postmortem samples. Yeasts may produce ethanol following trauma.3 Postmortem levels may be lower (cocaine) or higher (alcohol) than in-life levels TCAs, tricyclic antidepressants.

17 - Acting on clozapine plasma concentration resu

Acting on clozapine plasma concentration results

Pharmacokinetics CHAPTER 11 Acting on clozapine plasma concentration results In most developed countries, clozapine blood concentration monitoring is widely used. Table 11.4 gives some general advice about actions that should be taken when clozapine levels are 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 or exponentially related to dose or plasma level. That is, there is no step-change in the risk of seizures, for example, at a particular dose or plasma concentration.1 The same is broadly true of therapeutic effects. The likelihood of response in an individual increases from concentrations below the accepted therapeutic range up to around 1000mcg/L.2–4 Table 11.4 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 concentrations are reached,5 reducing over time as tolerance develops. Table 11.4 Recommended actions in response to clozapine concentrations.* Plasma concentration Response status Tolerability status Suggested action <350mcg/L Poor Poor Increase dose very slowly to give level of 350mcg/L Poor Good Increase dose to give level of 350mcg/L Good Poor Maintain dose. Consider cautious dose reduction if tolerability does not improve. Good Good Continue to monitor. No action required. 350–500mcg/L Poor Poor Increase dose slowly, according to tolerability, to give level of >500mcg/L. Consider prophylactic anticonvulsant.† If no improvement, consider augmentation. Poor Good Increase dose slowly, according to tolerability, to give level of >500mcg/L (up to 1000mcg/mL if tolerated). Consider prophylactic anticonvulsant.† If no improvement, consider augmentation. Good Poor Maintain dose to see if tolerability improves. Consider cautious dose reduction to give plasma level of around 350mcg/L. Good Good Continue to monitor. No action required. 500–1000mcg/L Poor Poor Consider use of prophylactic antiseizure drug.† Consider augmentation. Attempt dose reduction if augmentation successful. Poor Good Consider use of prophylactic antiseizure drug.† Slowly increase dose (up towards 1000mcg/mL if tolerated). Also consider augmentation. Good Poor Attempt slow dose reduction to give plasma level of 350–500mcg/L unless there is known non-response at lower level. If this is the case, maintain dose and consider adding anticonvulsant.† Optimise treatment of adverse effects. Good Good Consider use of prophylactic antiseizure drug.† Maintain dose if good tolerability continues.

(Continued)

18 - References

References

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> 1000mcg/L Poor Poor Add antiseizure drug. Attempt augmentation. Reduce dose to give level of <1000mcg/L. Consider abandoning clozapine treatment. Poor Good Add antiseizure drug. Attempt augmentation. If augmentation successful, reduce dose to give level <1000mcg/L. If unsuccessful, consider abandoning clozapine treatment. Good Poor Add antiseizure drug. Attempt slow dose reduction to give plasma level <1000mcg/L. Good Good Add antiseizure drug. Monitor closely; attempt dose reduction only if tolerability declines. Notes Poor response No response or unsatisfactory response to clozapine. For example, not sufficiently well to be discharged. Good response Obvious positive changes related to use of clozapine. Patient likely to be suitable for discharge to either supported or unsupported care in the community. Poor tolerability Dose constrained by adverse effects such as tachycardia, sedation, hypersalivation, hypotension, etc. (see Chapter 1 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 1). In all situations, ensure adequate treatment for clozapine-induced constipation. Constipation is dose-related. Ensure regular bowel movements and record bowel function. Stimulant laxatives such as senna are required (see Chapter 1). Seizures are dose- and plasma level-dependent. Suitable antiseizure agents are valproate, lamotrigine and, rarely, topiramate. Use lamotrigine if response is poor; valproate if affective symptoms are present (see Chapter 2). Note that use of valproate increases risk of neutropenia with clozapine.6 Both valproate and topiramate are contraindicated in women of child-bearing age. *This table applies to results for patients on a stable clozapine dose with confirmed good adherence. †Antiseizure drugs should usually be used in patients whose plasma level exceeds 600mcg/L, unless EEG is normal, and in those with lower plasma levels who experience clozapine-induced seizures.

19 - Psychotropic drugs and cytochrome (CYP) funct

Psychotropic drugs and cytochrome (CYP) function

Pharmacokinetics CHAPTER 11 Psychotropic drugs and cytochrome (CYP) function Information on the effect of drugs on CYP function helps predict or confirm suspected interactions that may not have been uncovered in regulatory trials or in clinical use. In addition to the effect of co--administered drugs on CYP function, genetic polymorphism associated with some enzymes may also account for inter-individual variations in the metabolism of certain drugs. Genetic variation influences both likelihood of response and tolerability (see later in this section for more information on genetic variation).1,2 The effects of polymorphism and pharmacokinetic interaction are difficult to predict because some drugs are metabolised by more than one enzyme and an alternative pathway(s) may compensate if other enzyme pathways are inhibited. A further complication is that CYPs are active in sites other than the liver (e.g. gut, brain). The effect of psychotropics on brain CYPs can be markedly different from hepatic CYPs.3 The function of CYPs is not the only consideration. P-glycoprotein (P-gp) is a drug transporter protein found in the gut wall. P-gp can eject (active process) drugs that diffuse (passive process) across the gut wall. P-gp is also found in testes and in the blood– brain barrier. Drugs that inhibit P-gp are anticipated to increase the uptake of other drugs (that are substrates for P-gp), and drugs that induce P-gp are anticipated to reduce the uptake of other drugs (that are substrates for P-gp). Many drugs that are substrates for CYP3A4 have also been found to be substrates for P-gp. Uridine diphosphate (UDP)--glucuronosyltransferase (UGT) has been identified as an enzyme that is responsible for phase II (conjugation) reactions. Valproate is a potent inhibitor of UGT, hence its interaction with lamotrigine, a drug which is primarily metabolised by UGT. UGT enzymes are also involved in the metabolism of lumateperone, olanzapine, topiramate and trifluoperazine. In Table 11.5, drugs highlighted in bold indicate: ■ ■Predominant metabolic enzyme pathway, or ■ ■Predominant enzyme activity (inhibition or induction). Drugs annotated with * are known to be a minor metabolic enzyme pathway or activity (i.e. not demonstrated to be clinically significant). Drugs in normal font (not bold and without *) indicate metabolic enzyme pathway(s) or activity where significance is

unclear or unknown. Table 11.5 does not include details of the effects of non-psychotropics on CYP function.

884 The Maudsley® Prescribing Guidelines in Psychiatry Table 11.5 Effects of psychotropics on CYP function. CYP1A2 Substrates Inhibitors Inducers Asenapine4 Agomelatine Amitriptyline* Bupropion* Caffeine Chlorpromazine Clomipramine* Clozapine Duloxetine Fluphenazine Fluvoxamine Haloperidol Imipramine* Levomepromazine Lumateperone Melatonin Mirtazapine* Olanzapine Perphenazine Pimozide* Ramelteon Zolpidem* CHAPTER 11 Moclobemide Perphenazine CYP2A6 Substrates Inhibitors Inducers Bupropion* Caffeine Nicotine CYP2B6 Substrates Inhibitors Inducers Bupropion Methadone* Nicotine Sertraline* Fluoxetine* Fluvoxamine Memantine Paroxetine* Sertraline* CYP2B7 Substrates Inhibitors Inducers Buprenorphine* Not known Not known 'Barbiturates' Carbamazepine Modafinil* Phenobarbital Phenytoin Fluvoxamine Iloperidone Levomepromazine Melatonin5 Tranylcypromine Phenobarbital Carbamazepine* Modafinil* Phenobarbital Phenytoin

Table 11.5 (Continued) CYP2C8 Substrates Inhibitors Inducers Lumateperone Zopiclone* Not known Not known CYP2C9 Substrates Inhibitors Inducers Fluoxetine* Fluvoxamine Modafinil Valproate Agomelatine* Amitriptyline Bupropion* Doxepin Fluoxetine* Lamotrigine Phenobarbital Phenytoin Sertraline* Valproate CYP2C19 Substrates Inhibitors Inducers Escitalopram* Fluoxetine Fluvoxamine Iloperidone Melatonin5 Agomelatine* Amitriptyline Atomoxetine Carbamazepine* Citalopram Clomipramine* Diazepam Escitalopram Fluoxetine* Imipramine* Melatonin Methadone Moclobemide Phenytoin Sertraline* Suvorexant Trimipramine* Valproate Moclobemide Modafinil Topiramate Pharmacokinetics CHAPTER 11 Carbamazepine SJW Carbamazepine SJW (Continued)

886 The Maudsley® Prescribing Guidelines in Psychiatry Table 11.5 (Continued) CYP2D6 Substrates Inhibitors Inducers 'Amfetamines' Amitriptyline Aripiprazole Atomoxetine CHAPTER 11 Brexpiprazole Cariprazine Chlorpromazine Citalopram Clomipramine Clozapine* Deutetrabenazine Donepezil* Doxepin Duloxetine Escitalopram Fluoxetine Fluphenazine Fluvoxamine Galantamine Haloperidol Iloperidone Imipramine Methadone* Mianserin Mirtazapine* Moclobemide Nortriptyline Olanzapine Paroxetine Perphenazine Pimavanserin Pimozide* Quetiapine* Risperidone Sertindole Sertraline Trazodone* Trimipramine Valbenazine Venlafaxine Vortioxetine Zuclopenthixol CYP2E1 Substrates Inhibitors Inducers Bupropion Ethanol Disulfiram Paracetamol Ethanol Amitriptyline Asenapine4 Not known Bupropion Chlorpromazine Citalopram* Clomipramine Clozapine Doxepin Duloxetine Escitalopram Fluoxetine Fluphenazine Fluvoxamine* Haloperidol Iloperidone Levomepromazine Methadone* Moclobemide Paroxetine Perphenazine Reboxetine* Risperidone Sertraline* Venlafaxine* Ziprasidone*

Table 11.5 (Continued) CYP3A4 Substrates Inhibitors Inducers Alfentanyl Alprazolam Amitriptyline Aripiprazole Atomoxetine* Fluoxetine Fluvoxamine Iloperidone Blonaserin Brexipiprazole Buprenorphine Bupropion* Buspirone Carbamazepine Cariprazine Chlorpromazine Citalopram Clomipramine* Clonazepam Clozapine* Diazepam Donepezil Dosulepin Escitalopram* Fentanyl Fluoxetine* ?Flurazepam Galantamine Haloperidol Imipramine Lemborexant Levomepromazine Lumateperone Lurasidone Methadone Midazolam Mirtazapine Modafinil Nitrazepam Paliperidone Perphenazine Pimavanserin Pimozide Quetiapine Reboxetine Risperidone* Sertindole Sertraline* Suvorexant Trazodone Trimipramine* Valbenazine Venlafaxine Vilazodone Zaleplon Ziprasidone Zolpidem Zopiclone Zuclopenthixol Levomepromazine Paroxetine Perphenazine Reboxetine*

Ziprasidone* Note: information on CYP function is derived from individual SPCs and US labelling (accessed August 2024), from systematic reviews7,8 and the Flockhart table.9 SJW, St John’s wort; SPC, summary of product characteristics. Asenapine? Carbamazepine Clozapine6 Levomepromazine6 Modafinil Phenobarbital ‘and probably other barbituates’ Phenytoin SJW Topiramate CHAPTER 11

20 - Genetics of cytochrome function

Genetics of cytochrome function

888 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 11 Genetics of cytochrome function The function of CYPs is under genetic control. Each individual's CYP function is determined by heredity and is often, but not always, linked to ethnicity. Phenotypes are usually described as poor metabolisers, intermediate metabolisers, normal metabolisers and rapid or ultrarapid metabolisers. Table 11.6 gives the approximate distribution of phenotypes across nine ethnicities. Awareness of differences in phenotype frequencies can help predict and understand drug metabolism differences. As an example, CYP1A2 ultrarapid metaboliser phenotypes are most often seen in African Americans and so we might expect a higher rate of clozapine failure (or at least low plasma levels) in this population.

Table 11.6 Estimated phenotype frequency by ancestry for CYP1A2, CYP2D6, CYP2C19, CYP2C9 and CYP3A4.10–22 Genotype-predicted phenotypes African10,11 African American12,13 European ancestry + North American14 Near Eastern East Asian South/Central Asian Americas Latino15 Oceanian CYP1A2 Ultrarapid metaboliser 10–20% 15–30% 1–4% 5–10% 1–5% 3–8% 5–10% 7–12% 5–10% Normal metaboliser 55–70% 50–60% 70–80% 65–75% 65–75% 60–70% 60–70% 65–75% 65–75% Intermediate metaboliser 10–20% 10–15% 10–15% 10–15% 10–20% 10–15% 10–15% 10–15% 10–15% Poor metaboliser 5–10% 5–10% 5–10% 5–10% 10–15% 10–15% 5–10% 5–10% 5–10% CYP2D6 Ultrarapid metaboliser 4% 5% 3% 10% 1% 2% 6% 4% 20% Normal metaboliser 43% 56% 51% 55% 52% 62% 64% 59% 67% Intermediate metaboliser 44% 36% 39% 30% 39% 30% 24% 29% 10% Poor metaboliser 2% 2% 7% 2% 1% 2% 2% 3% 0% CYP2C19 Ultrarapid metaboliser 3% 4% 5% 4% 0% 3% 1% 3% 0% Rapid metaboliser 19% 24% 27% 26% 3% 19% 14% 24% 2% Normal metaboliser 30% 33% 40% 45% 38% 30% 63% 53% 4% Intermediate metaboliser 36% 31% 26% 24% 46% 41% 21% 19% 37% Likely intermediate metaboliser 4% 3% 0% 0% 0% 0% 0% 0% 0% Poor metaboliser 6% 4% 2% 2% 13% 8% 2% 1% 57% Likely poor metaboliser 1% 1% 0% 0% 0% 0% 0% 0% 0% CYP2C9 Normal metaboliser 73% 76% 63% 61% 84% 60% 83% 75% 91% (Continued)

Table 11.6 (Continued) Genotype-predicted phenotypes African10,11 African American12,13 European ancestry + North American14 Near Eastern East Asian South/Central Asian Americas

Latino15 Oceanian Intermediate metaboliser 26% 24% 35% 36% 15% 36% 16% 25% 9% Poor metaboliser 1% 1% 3% 3% 1% 4% 0% 1% 0% CYP3A4 Ultrarapid metaboliser 7–15% 10–15% 1–5% 5–10% 1–4% 2–6% 4–9% 3–8% 4–10% Normal metaboliser 50–65% 55–70% 65–75% 60–70% 60–75% 60–70% 55–65% 60–70% 60–70% Intermediate metaboliser 15–25% 10–20% 15–20% 15–20% 15–25% 15–20% 15–20% 15–20% 15–20% Poor metaboliser 5–10% 5–10% 5–10% 5–10% 5–10% 5–10% 5–10% 5–10% 5–10%

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22 - Smoking and psychotropic drugs

Smoking and psychotropic drugs

892 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 11 Smoking and psychotropic drugs Tobacco smoke contains polycyclic aromatic hydrocarbons that induce certain hepatic enzymes (CYP1A2 in particular).1 Other enzymes that may be induced by smoking are CYP2C19 and, possibly, CYP3A4 and some variants of UGT (glycosyltransferases).2 The extent of enzyme induction is determined by the number and type of cigarettes smoked and by the degree of smoke inhalation.3 For some drugs used in psychiatry, smoking significantly reduces drug plasma levels and higher doses are required than in non-smokers. Smoking may also affect alcohol metabolism by inducing CYP2E1.3 When people stop smoking, enzyme activity halves roughly every 2 days.4 It is very important to appreciate that nicotine replacement and vaping have no effect on this process (they do not contain polycyclic aromatic hydrocarbons). Plasma levels of affected drugs will then rise, sometimes substantially. Dose reduction will usually be necessary. If smoking is restarted, enzyme activity increases, plasma levels fall and dose increases are then required. The process is complicated, and effects are difficult to predict. Of course, few people manage to give up smoking completely, so additional complexity is introduced by intermittent smoking and repeated attempts at stopping completely. Close monitoring of plasma levels (where useful), clinical progress and adverse effect severity are essential. Table 11.7 gives details of psychotropic drugs known to be affected by smoking status. Table 11.7 Effect of smoking on psychotropic drugs. Drug Effect of smoking Action to be taken on stopping smoking Action to be taken on restarting smoking Agomelatine5 Plasma levels reduced Monitor closely. Dose may need to be reduced. Consider reintroducing previous smoking dose. Benzodiazepines3,6 Plasma levels reduced by 0–50% (depends on drug and smoking status) Monitor closely. Consider reducing dose by up to 25% over 1 week. Monitor closely. Consider restarting ‘normal’ smoking dose. Carbamazepine3 Unclear, but smoking may reduce carbamazepine plasma levels to a small extent. Monitor for changes in severity of adverse effects. Monitor plasma levels. Chlorpromazine3,6,7 Plasma levels reduced. Varied estimates of exact effect. Monitor closely. Consider dose reduction. Monitor closely. Consider restarting previous smoking dose. Clozapine8–10 Reduces plasma levels by up to 50%. Effect may be maximal at as few as 2–5 cigarettes a day.11 Plasma level reduction and risk of relapse may be greater in those receiving valproate.12 Effect is reversed by co-administered fluvoxamine.13 Take plasma level before stopping. On stopping, reduce dose gradually (over a

week) until around 75% of original dose is reached (i.e. reduce by 25%). Repeat plasma level 1 week after stopping. Anticipate further dose reductions. Take plasma level before restarting. Increase dose to previous smoking dose over 1 week. Repeat plasma level. Deterioration is common if dose increases allow a fall in blood levels.14 Duloxetine15,16 Plasma levels may be reduced by up to 50%. Monitor closely. Dose may need to be reduced. Consider reintroducing previous smoking dose.

Pharmacokinetics CHAPTER 11 Table 11.7 (Continued) Drug Effect of smoking Action to be taken on stopping smoking Action to be taken on restarting smoking Escitalopram17 In practice, smokers have lower blood levels despite being given higher doses. Reduction in levels may be up to 50% (possibly via induction of CYP2C19). Monitor closely. Consider 25% dose reduction. Monitor closely. Reinstate smoking dose. Fluphenazine18 Reduces plasma levels by up to 50% On stopping, reduce dose by 25%. Monitor carefully over following 4–8 weeks. Consider further dose reductions. On restarting, increase dose to previous smoking dose. Fluvoxamine19 Plasma levels decreased by around a third Monitor closely. Dose may need to be reduced. Dose may need to be increased to previous level. Haloperidol20,21 Reduces plasma levels by around 25–50% Reduce dose by around 25%. Monitor carefully. Consider further dose reductions. On restarting, increase dose to previous smoking dose. Loxapine22 (inhaled) Half-life reduced from 15.7 to 13.6 hours Monitor Monitor Mirtazapine23 Unclear, but effect probably minimal Monitor Monitor Olanzapine10,24–26 Reduces plasma levels by up to 50%. Effect increases with number of cigarettes smoked.26 Take plasma level before stopping. On stopping, reduce dose by 25%. After 1 week, repeat plasma level. Consider further dose reductions. Take plasma level before restarting. Increase dose to previous smoking dose over 1 week. Repeat plasma level. Risperidone2,27 Active moiety concentrations probably lower in smokers. Minor effect (possibly via induction of CYP3A4). Smoking may not affect paliperidone concentrations.28 Monitor closely Monitor closely Trazodone29 Around 25% reduction Monitor for increased sedation. Consider dose reduction. Monitor closely. Consider increasing dose. Tricyclic antidepressants3,6,30 Plasma levels reduced by 25–50%. Some studies suggest more limited effect.2,31 Monitor closely. Consider reducing dose by 10–25% over 1 week. Consider further dose reductions. Monitor closely. Consider restarting previous smoking dose. Zuclopenthixol32,33 Unclear, but effect probably minimal Monitor Monitor Note (again: it bears repeating): only tobacco smoking induces hepatic enzymes in the manner described above. This includes cigarettes and cannabis/tobacco ‘joints’. Nicotine replacement, vaping devices and electronic cigarettes (which do not contain polycyclic aromatic compounds) have no effect on enzyme activity.34,35

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24 - Drug interactions with alcohol

Drug interactions with alcohol

25 - Pharmacokinetic interactions14

Pharmacokinetic interactions1–4

Pharmacokinetics CHAPTER 11 Drug interactions with alcohol Drug interactions with alcohol are complex. Many patient-related and drug-related factors need to be considered. It can be difficult to predict outcomes accurately because a number of processes may occur simultaneously or consecutively. Pharmacokinetic interactions1–4 Alcohol (ethanol) is absorbed from the gastrointestinal tract and distributed in body water. The volume of distribution is smaller in women and the elderly where plasma levels of alcohol will be higher than in young males for a given intake of alcohol. Ingested alcohol is subject to metabolism by alcohol dehydrogenase (ADH). A small proportion of alcohol is metabolised by ADH in the stomach. The remainder is metabolised in the liver by ADH, and by CYP2E1. At low alcohol concentrations only ADH is active; CYP2E1 only begins to contribute when concentrations approach the legal driving limit of many countries (0.08%).5 CYP2E1 plays a minor role in occasional drinkers but is an important and inducible metabolic route in chronic, heavy drinkers. The induction of CYP2E1 accounts for the apparent tolerance of alcohol in heavy drinkers.6 CYP1A2, CYP3A4 and many other CYP enzymes also play a minor role in the metabolism of ethanol.7,8 CYP2E1 and ADH convert alcohol to acetaldehyde. This is both the toxic substance responsible for the unpleasant symptoms of the ‘Antabuse reaction’ (e.g. flushing, headache, nausea, malaise) and the compound implicated in hepatic damage. It may have psychotropic effects – ethanol is metabolised to acetaldehyde by CYP2E1 in the brain.9 The enzyme catalase is also known to metabolise alcohol to acetaldehyde in the brain and elsewhere.10 Acetaldehyde is further metabolised by aldehyde dehydrogenase to acetic acid and then to carbon dioxide and water (Figure 11.1).

- This is a minor route in occasional drinkers, and a major route in heavy drinkers and at higher blood alcohol concentration. The ubiquitous enzyme catalase is also able to metabolise ethanol but its overall contribution is not known. Alcohol dehydrogenase (ADH) CYP2E1* Aldehyde dehydrogenase Ethanol Acetaldehyde Ethanoic acid CYP3A4 CYP1A2 Water + CO2 CYP2B6 Figure 11.1 Metabolism of alcohol.

 All of the enzymes involved in the metabolism of alcohol exhibit genetic polymorphism. For example, the majority of people of

north Asian origin are poor metabolisers via aldehyde dehydrogenase.11 Enzyme function can change in response to alcohol. Chronic consumption of alcohol induces CYP2E1 and CYP3A4. The effects of alcohol on other hepatic metabolising enzymes have been poorly studied. Table 11.8 lists drugs that inhibit ADH and aldehyde dehydrogenase. Interactions are difficult to predict in alcohol misusers because two opposing processes may be at work: competition for enzymatic sites during periods of consumption/ intoxication (increasing drug plasma levels) and enzyme induction prevailing during periods of sobriety (reducing drug plasma levels10). In chronic drinkers, particularly those who binge-drink, blood levels of prescribed drugs may reach toxic levels during periods of intoxication with alcohol and then be sub-therapeutic when the patient is sober. Even in non-intoxicated individuals there is some evidence that co-administered alcohol confers competitive inhibition of CYP3A4, leading to increased exposure to drugs metabolised by this enzyme (Table 11.9).15 This makes it very difficult to optimise treatment of physical or mental illness. Table 11.8 Drugs that inhibit alcohol dehydrogenase and aldehyde dehydrogenase. Enzyme Inhibited by Potential consequences Alcohol dehydrogenase Aspirin H2 antagonists Reduced metabolism of alcohol resulting in higher plasma levels for longer periods of time Aldehyde dehydrogenase Chlorpropamide Disulfiram Griseofulvin Isoniazid Isosorbide dinitrate Metronidazole* Nitrofurantoin Sulphamethoxazole Tolbutamide Reduced ability to metabolise acetaldehyde leading to ‘Antabuse’ type reaction: facial flushing, headache, tachycardia, nausea and vomiting, arrhythmias and hypotension *Evidence that metronidazole has any effect on aldehyde dehydrogenase is surprisingly weak.12–14 Table 11.9 Co-administration of alcohol and substrates for CYP2E1 and CYP3A4.5,6,16 Substrates for enzyme (note: this is not an exhaustive list) Effects in an intoxicated patient Effects in a chronic, sober drinker CYP2E1 Isoniazid Paracetamol Phenobarbitone Warfarin Zopiclone Competition between alcohol and drug leading to reduced rates of metabolism of both compounds. Increased plasma levels may lead to toxicity Activity of CYP2E1 is increased up 10-fold Increased metabolism of drugs potentially leading to therapeutic failure

26 - Pharmacodynamic interactions24

Pharmacodynamic interactions2–4

Pharmacokinetics CHAPTER 11 Interactions of uncertain aetiology include increased blood alcohol concentrations in people who take verapamil and decreased metabolism of methylphenidate in people who consume alcohol. Alcohol may also, via various routes, impair the function of slow--release tablet mechanisms causing dose-dumping.17 Pharmacodynamic interactions2–4 Alcohol enhances inhibitory neurotransmission at gamma-aminobutyric acid A (GABA-A) receptors and reduces excitatory neurotransmission at glutamate N-methyl-D-aspartate (NMDA) receptors. It also increases dopamine release in the mesolimbic pathway and may have some effects on serotonin and opiate pathways. Given these actions, alcohol would be expected to cause sedation, amnesia and ataxia (Table 11.10) and give rise to feelings of pleasure (and/or worsen psychotic symptoms in vulnerable individuals). Table 11.9 (Continued) Substrates for enzyme (note: this is not an exhaustive list) Effects in an intoxicated patient Effects in a chronic, sober drinker CYP3A4 Alprazolam Aripiprazole Benzodiazepines Carbamazepine Clozapine Donepezil Galantamine Haloperidol Methadone Mirtazapine Quetiapine Risperidone Sildenafil Tricyclics Valproate Venlafaxine Z-hypnotics Competition between alcohol and drug leading to reduced rates of metabolism of both compounds. Increased plasma levels may lead to toxicity Increased rate of drug metabolism potentially leading to therapeutic failure Enzyme induction can last for several weeks after alcohol consumption ceases Table 11.10 Pharmacodynamic interactions with alcohol. Effect of alcohol Effect exacerbated by Potential consequences Sedation Other sedative drugs, e.g.: Antihistamines Antipsychotics Baclofen Benzodiazepines Lofexidine Opiates Tizanidine Tricyclics Z--hypnotics Increased CNS depression ranging from increased propensity to be involved in accidents through to respiratory depression and death (Continued)

898 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 11 Alcohol can cause or worsen psychotic symptoms by increasing dopamine release in mesolimbic pathways. The effect of antipsychotic drugs may be competitively antagonised, rendering them less effective. Electrolyte disturbances secondary to alcohol-related dehydration can be exacerbated by other drugs that cause electrolyte disturbances (e.g. diuretics). Heavy alcohol consumption can lead to hypoglycaemia in people with diabetes who take insulin or oral hypoglycaemics. Theoretically there is an increased risk of lactic acidosis in patients who take metformin with alcohol. Alcohol can also

increase blood pressure. Chronic alcohol drinkers are particularly susceptible to the gastrointestinal irritant effects of aspirin and non-steroidal anti-inflammatory drugs. In the presence of pharmacokinetic interactions, pharmacodynamic interactions may be more marked. For example, in a chronic heavy drinker who is sober, enzyme induction will increase the metabolism of diazepam, which may lead to increased levels of anxiety (treatment failure). If the same patient becomes intoxicated with alcohol, the metabolism of diazepam will be greatly reduced as it will have to compete with alcohol for the metabolic capacity of CYP3A4. Plasma levels of alcohol and diazepam will rise (toxicity). As both alcohol and diazepam are sedative (via GABA-A affinity), loss of consciousness and respiratory depression may occur. Table 11.11 lists drugs that are safe and those that should be avoided in patients who continue drinking. Table 11.10 (Continued) Effect of alcohol Effect exacerbated by Potential consequences Amnesia Other amnesic drugs, e.g.: Barbiturates Benzodiazepines Z-hypnotics Increased amnesic effects ranging from mild memory loss to total amnesia. Usually anterograde amnesia: loss of memory of events after the effects of alcohol begin Ataxia ACE inhibitors Beta-blockers Calcium channel blockers Nitrates Adrenergic alpha receptor antagonists, e.g.: Clozapine Risperidone Tricyclics Increased unsteadiness and falls ACE, angiotensin-converting enzyme; CNS, central nervous system.

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17. Lennernäs H. Ethanol-drug absorption interaction: potential for a significant effect on the plasma pharmacokinetics of ethanol vulnerable formulations. Mol Pharm 2009; 6:1429–1440. Table 11.11 Psychotropic drugs: choice in patients who continue to drink. Safest choice Best avoided Antipsychotics Sulpiride and amisulpride Paliperidone, if depot required (non-sedative and renally excreted) Very sedative antipsychotics such as chlorpromazine and clozapine Antidepressants SSRIs – citalopram, sertraline Potent inhibitors of CYP3A4 (fluoxetine, paroxetine) may decrease alcohol metabolism in chronic drinkers TCAs, because impairment of metabolism by alcohol (while intoxicated) can lead to increased plasma levels and consequent signs and symptoms of overdose (profound hypotension, seizures, arrhythmias and coma) Cardiac effects can be exacerbated by electrolyte disturbances Combinations of TCAs and alcohol profoundly impair psychomotor skills Mirtazapine – often very sedative MAOIs, as can cause profound hypotension. Also potential interaction with tyramine-containing drinks which can lead to hypertensive crisis Mood stabilisers Valproate (where regulations allow) Carbamazepine Higher plasma levels achieved during periods of alcohol intoxication may be poorly tolerated Lithium, because it has a narrow therapeutic index and alcohol-related dehydration and electrolyte disturbance can precipitate lithium toxicity Note: be aware of the possibility of hepatic failure or reduced hepatic function in chronic alcohol misusers. See ‘Hepatic impairment’ in Chapter 8. Also note the risk of hepatic toxicity with some recommended drugs (e.g. valproate). MAOIs, monoamine oxidase inhibitors; TCAs, tricyclic antidepressants.