# 01 - Biochemical and haematological effects of psy

# Biochemical and haematological effects of psychotropics


Chapter 15 Biochemical and haematological effects of psychotropics Almost all psychotropics have haematology- or biochemistry-related adverse effects that may be detected using routine blood tests. While many of these changes are idiosyncratic and not clinically significant, others, such as the agranulocytosis associated with agents such as clozapine, will require regular monitoring of the full blood count. In general, where an agent has a high incidence of biochemical/haematological adverse effects or a rare but potentially fatal effect, regular monitoring is required as discussed in other sections. For other agents, laboratory-related adverse effects are comparatively rare (prevalence usually less than 1%), are often reversible upon cessation of the putative offending agent and are not always clinically significant. It should further be noted that medical comorbidity, polypharmacy and the effects of non-prescribed agents including substances of abuse and alcohol may also influence biochemical and haematological parameters. In some cases, where a clear temporal association between starting the agent and the onset of laboratory changes is unclear, then withdrawal and rechallenge with the agent in question may be considered. Where there is doubt as to the aetiology and significance of the effect, the appropriate source of expert advice should always be consulted. Tables 15.1 and 15.2 summarise those agents with identified biochemical and haematological effects from information compiled from various sources.1–9 In many cases the evidence for these various effects is limited, with information obtained mostly from case reports, case series and information supplied by manufacturers. For further details about each individual agent, the reader is encouraged to consult the appropriate section of this book as well as

other specialist sources, particularly product literature relating to individual drugs. Miscellany

960 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 15 Table 15.1 Summary of biochemical changes associated with psychotropics. Parameter Reference range10 Agents reported to raise levels Agents reported to lower levels Alanine aminotransferase (ALT) F: ≤34U/L M: ≤45U/L (may be higher in obesity) Antipsychotics: asenapine, benperidol, cariprazine, clozapine, haloperidol, loxapine, lumateperone tosylate, olanzapine, phenothiazines, quetiapine, risperidone/paliperidone Antidepressants: agomelatine, bupropion, MAOIs, mianserin, mirtazapine, SNRIs, SSRIs (especially paroxetine and sertraline), TCAs, trazodone, vortioxetine Anxiolytics/hypnotics: barbiturates, benzodiazepines, buspirone, clomethiazole, promethazine, suvorexant, tasimelteon, zolpidem Mood stabilisers: carbamazepine, lamotrigine, valproate Other: alcohol, atomoxetine, beta-blockers, caffeine, cocaine, disulfiram, naltrexone, opioids, stimulants (abused) Vigabatrin Albumin 35–50g/L (gradually decreases after age 40) Microalbuminuria may be a feature of metabolic syndrome secondary to psychotropic use (especially phenothiazines, clozapine, olanzapine and possibly quetiapine) Chronic use of amfetamine or cocaine Alkaline phosphatase 50–120U/L Baclofen, beta-blockers, benzodiazepines, caffeine (excess/chronic use), carbamazepine, citalopram, clozapine, disulfiram, duloxetine, galantamine, haloperidol, loxapine, memantine, modafinil, nortriptyline, olanzapine, phenytoin, sertraline, topiramate, trazodone, valbenazine, valproate; also associated with agents causing NMS Buprenorphine, fluoxetine (in children), zolpidem (rarely) Ammonia 11–32µmol/L (increased following meals and exercise) Barbiturates, carbamazepine, tobacco smoking, topiramate, valproate (may present with signs of encephalopathy) None known

Miscellany CHAPTER 15 Table 15.1 (Continued ) Parameter Reference range10 Agents reported to raise levels Agents reported to lower levels Amylase 28–100U/L Alcohol (acute), donepezil, opioids, pregabalin, rivastigmine, SSRIs (rarely) Agents associated with pancreatitis: alcohol, carbamazepine, clozapine, olanzapine, valproate None known Aspartate aminotransferase (AST) F: ≤34U/L M: ≤45U/L As for ALT; baclofen. Note: ALT is preferred as an indicator of liver damage Trifluoperazine, vigabatrin Bicarbonate 22–29mmol/L Laxative abuse Agents associated with SIADH: all antidepressants, antipsychotics (clozapine, haloperidol, olanzapine, phenothiazines, pimozide, risperidone/paliperidone, quetiapine); carbamazepine; also associated with agents causing metabolic acidosis (alcohol, cocaine, topiramate, zonisamide) Bilirubin ≤21µmol/L (total) Amitriptyline, atomoxetine, benzodiazepines, carbamazepine, chlordiazepoxide, chlorpromazine, citalopram, clomethiazole, clozapine, disulfiram, fluphenazine, imipramine, lamotrigine, meprobamate, milnacipran, olanzapine, phenothiazines, phenytoin, promethazine, sertraline, valbenazine, valproate; also associated with agents causing cholestasis/ hepatic damage Barbiturates C-reactive protein <10mg/L Buprenorphine (rare); also associated with agents causing myocarditis (clozapine) None known Calcium 2.20–2.60mmol/L (total, adjusted) 1.15–1.34mmol/L (ionised) Lithium (rare) Barbiturates, carbamazepine, haloperidol, valproate Carbohydrate-deficient transferrin (CDT) ≤1.5% Alcohol (CDT levels of 1.6–1.9% suggest high intake; levels ≥2% suggest excessive intake) None known (Continued )

962 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 15 Table 15.1 (Continued ) Parameter Reference range10 Agents reported to raise levels Agents reported to lower levels Chloride 95–108mmol/L Agents causing hyperchloraemic metabolic acidosis: topiramate, zonisamide Medications associated with SIADH: all antidepressants, antipsychotics (clozapine,

haloperidol, olanzapine, phenothiazines, pimozide, risperidone/paliperidone, quetiapine); carbamazepine, laxative abuse Cholesterol (total) ≤5.2mmol/L (usually compared with recommended action limits rather than reference ranges) Antipsychotics, especially those implicated in the metabolic syndrome (clozapine, olanzapine, phenothiazines, quetiapine). Rarely: aripiprazole, beta-blockers (additive effects with clozapine), carbamazepine, disulfiram, duloxetine, memantine, mirtazapine, modafinil, phenytoin, rivastigmine, sertraline, venlafaxine Prazosin, thyroid agents Creatine kinase F: 25–200U/L M: 40–320U/L (range for people of European descent; may be higher in other ethnic groups) Bremelanotide, brexpiprazole, cariprazine, clonidine, clozapine (when associated with seizures), cocaine, dexamfetamine, donepezil, lumateperone, olanzapine, pregabalin; also associated with agents causing NMS and SIADH; agents administered intramuscularly None known Creatinine F: 55–100µmol/L M: 60–120µmol/L Clozapine, lithium, lurasidone, thioridazine, valproate; medications associated with rhabdomyolysis (benzodiazepines, dexamfetamine, pregabalin, thioridazine); also associated with agents causing renal impairment, NMS and SIADH None known Ferritin F: 15–150mcg/L M: 30–400mcg/L (increases with age) Alcohol (acutely and in alcoholic liver disease) None known

Miscellany CHAPTER 15 Table 15.1 (Continued ) Parameter Reference range10 Agents reported to raise levels Agents reported to lower levels Gamma-glutamyl transferase (GGT) F: ≤38U/L M: ≤55U/L (limits twofold higher in persons of African ancestry) Antidepressants: mirtazapine, SSRIs (paroxetine and sertraline implicated), TCAs, trazodone, venlafaxine Anticonvulsants/mood stabilisers: carbamazepine, lamotrigine, phenobarbitone, phenytoin, valproate Antipsychotics: benperidol, chlorpromazine, clozapine, fluphenazine, haloperidol, olanzapine, quetiapine Other: alcohol, barbiturates, clomethiazole, dexamfetamine, modafinil, tobacco smoking None known Glucose Fasting: 2.8–6.1mmol/L Random: <11.1mmol/L Antidepressants: MAOIs, SSRIs/SNRIs,* TCAs* Antipsychotics: chlorpromazine, clozapine, haloperidol,* olanzapine,* quetiapine and others Substances of abuse: amfetamine, methadone, opioids Other: baclofen, beta- blockers,* bupropion,* caffeine* (in diabetics), clonidine, dexmedetomidine,* donepezil, gabapentin, galantamine, lithium,* nicotine, sympathomimetics, thyroid agents, valbenazine Alcohol; rarely with duloxetine, haloperidol, pregabalin, TCAs Medications associated with metabolic syndrome may result in raised or decreased glucose levels HbA1c 20–39mmol/mol Lithium, MAOIs, SSRIs Lactate dehydrogenase 90–200U/L (levels rise gradually with age) Benzodiazepines, clozapine, methadone, TCAs (especially imipramine), valproate; also associated with agents causing NMS None known Lipoproteins: HDL

> 1.2mmol/L Carbamazepine, nicotine, phenobarbital, phenytoin Beta-blockers, olanzapine, phenothiazines, valproate Lipoproteins: LDL <3.5mmol/L Beta--blockers, caffeine (controversial), carbamazepine, chlorpromazine, clozapine, iloperidone, memantine, mirtazapine, modafinil, olanzapine, phenothiazines, quetiapine, risperidone/ paliperidone, rivastigmine, venlafaxine Prazosin (Continued )

 CHAPTER 15 Table 15.1 (Continued ) Parameter Reference range10 Agents reported to raise levels Agents reported to lower levels Phosphate 0.8–1.5mmol/L Dexamfetamine; also associated with agents causing NMS

Carbamazepine, lithium, mianserin, topiramate Potassium 3.5–5.3mmol/L Beta-blockers, lithium Alcohol, disulfiram, caffeine, cocaine, haloperidol, lithium, mianserin, pregabalin, reboxetine, rivastigmine, sodium oxybate, sympathomimetics, topiramate, zonisamide; may also be a feature of delirium tremens Prolactin Normal: <350mU/L Abnormal:

> 600mU/L Antidepressants: especially amoxapine, MAOIs and TCAs; SSRIs and venlafaxine also implicated Antipsychotics: amisulpride, haloperidol, pimozide, risperidone/paliperidone, sulpiride and others (aripiprazole,† asenapine, brexpiprazole, cariprazine, clozapine, lurasidone, olanzapine, quetiapine and ziprasidone have minimal effects on prolactin levels) Other: benzodiazepines, buspirone, deutetrabenazine, opioids, ramelteon, tetrabenazine, valbenazine Aripiprazole, dopamine agonists, pirenzepine Protein (total) 60–80g/L None known Olanzapine (rarely) Sodium 133–146mmol/L Lithium (in overdose) Antidepressants: especially SSRIs/ SNRIs; others also implicated – see section on hyponatraemia in Chapter 3 Antipsychotics: all (via SIADH) Mood stabilisers: carbamazepine, lithium, valproate Other: benzodiazepines, clonidine, donepezil, memantine, rivastigmine Testosterone F: 0.22–2.9nmol/L M: 9.9–27.8nmol/L Diazepam Opioids, ramelteon Thyroid- stimulating hormone 0.3–4.0mU/L Aripiprazole, carbamazepine, lithium, quetiapine, rivastigmine, sertraline, valproate (slightly) Moclobemide, thyroid agents Thyroxine Free: 9–26pmol/L Total: 60–150nmol/L Rarely; amfetamine (heavy abuse), moclobemide, propranolol Barbiturates, carbamazepine, liothyronine, lithium (causes decreased T4 secretion), opioids, phenytoin, valproate. Rarely implicated: aripiprazole, clozapine, quetiapine, rivastigmine, sertraline

Miscellany CHAPTER 15 Table 15.2 Summary of haematological changes associated with psychotropics. Parameter Reference range Agents reported to raise counts/levels Agents reported to lower counts/levels Activated partial thromboplastin time 23–33 seconds Phenothiazines (especially chlorpromazine) Modafinil (rare) Basophils 0.0–0.1×109/L Clozapine, TCAs (especially desipramine) None known Eosinophils 0.04–0.40×109/L Amoxapine, beta--blockers, bupropion, buspirone, carbamazepine, chloral hydrate, chlorpromazine, clonazepam, clozapine, donepezil, fluphenazine, haloperidol, loxapine, meprobamate, maprotiline, methylphenidate (IV abuse only), modafinil, naltrexone (parenterally administered), olanzapine, promethazine, quetiapine, risperidone/ paliperidone, SSRIs, TCAs, tetrazepam, tryptophan,* valproate, venlafaxine; may also be a feature of agents causing a hypersensitivity syndrome None known Table 15.1 (Continued ) Parameter Reference range10 Agents reported to raise levels Agents reported to lower levels Triglycerides None known Triiodothyronine Free: 3.0–6.8pmol/L Total: 1.2–2.9nmol/L Heroin, methadone Free T3: valproate Total T3: carbamazepine, lithium, propranolol Urate (uric acid) F: 0.16–0.36mmol/L M: 0.21–0.43mmol/L (increases with age) Alcohol (acute), caffeine (false positive), clozapine, levodopa, olanzapine, pindolol, prazosin, topiramate, zonisamide Sertraline (slightly) Urea 2.5–7.8 mmol/L (increases with age) Carbamazepine, levodopa; rarely with agents associated with anticonvulsant hypersensitivity syndrome and rhabdomyolysis None known *May also be associated with hypoglycaemia. †May also be associated with subnormal prolactin levels. F, female; HbA1c, haemoglobin A1c; HDL, high-density lipoprotein;

LDL, low-density lipoprotein; M, male; MAOIs, monoamine oxidase inhibitors; NMS, neuroleptic malignant syndrome; SIADH, syndrome of inappropriate antidiuretic hormone; TCAs, tricyclic antidepressants. (Continued )

966 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 15 Table 15.2 (Continued ) Parameter Reference range Agents reported to raise counts/levels Agents reported to lower counts/levels Erythrocyte sedimentation rate F: 1–12mm/h M: 1–10mm/h (increases with age) Clozapine, dexamfetamine, levomepromazine, maprotiline, SSRIs Buprenorphine Haemoglobin F: 115–165g/L M: 130–180g/L Clozapine, testosterone, tobacco smoking Aripiprazole, barbiturates, buprenorphine, bupropion, carbamazepine, chlordiazepoxide, chlorpromazine, donepezil, duloxetine, galantamine, MAOIs, memantine, meprobamate, mianserin, phenytoin, promethazine, rivastigmine, tramadol, trifluoperazine, vigabatrin Lymphocytes 1.5–4.5×109/L Naltrexone, opioids, tobacco smoking, valproate; may also be a feature of drugs causing hypersensitivity syndrome Alcohol (chronic), chloral hydrate, clozapine, lithium, mirtazapine (rarely) Mean cell haemoglobin 27–32pg Medications associated with megaloblastic anaemia, e.g. all anticonvulsants, nitrous oxide None known Mean cell haemoglobin concentration 320–360g/L Mean cell volume 80–100fL Alcohol Monocytes 0.2–0.8×109/L Haloperidol None known Neutrophils 2.0–7.5×109/L (may be lower in people of African descent owing to benign ethnic neutropenia) Bupropion, carbamazepine,† citalopram, chlorpromazine, clozapine,† duloxetine, fluoxetine, fluphenazine, haloperidol, lamotrigine, lithium, maprotiline, olanzapine, quetiapine, risperidone/paliperidone, rivastigmine, tiotixene, trazodone, venlafaxine Agents associated with agranulocytosis: amoxapine, aripiprazole, barbiturates, carbamazepine, chlordiazepoxide, chlorpromazine, clozapine,‡ cocaine (adulterated), diazepam, fluphenazine, haloperidol, meprobamate, mianserin, mirtazapine, olanzapine, pirenzepine, promethazine, risperidone/paliperidone, TCAs (especially imipramine), tranylcypromine, valproate Agents associated with leucopenia: amitriptyline, amoxapine, asenapine, bupropion, carbamazepine, cariprazine, chlorpromazine, citalopram, clomipramine, clonazepam, clozapine, duloxetine, fluoxetine, fluphenazine, galantamine, haloperidol, lamotrigine, lorazepam, lumateperone, lurasidone, memantine, meprobamate, mianserin, mirtazapine, modafinil, nitrous oxide, olanzapine, oxazepam, phenelzine, pregabalin, promethazine, quetiapine, tranylcypromine, valproate, venlafaxine, ziprasidone Agents associated with neutropenia: clozapine, sertraline, trazodone, valproate Packed cell volume F: 0.37–0.47L/L M: 0.40–0.52L/L Clozapine (rare), testosterone Benzodiazepines (rare), buprenorphine, naltrexone, vigabatrin

Miscellany CHAPTER 15 Table 15.2 (Continued ) Parameter Reference range Agents reported to raise counts/levels Agents reported to lower counts/levels Platelets 150–450×109/L Lamotrigine, lithium† Alcohol, barbiturates, beta-blockers, benzodiazepines, bupropion, buspirone, carbamazepine, chlordiazepoxide, chlorpromazine, clonazepam, clonidine, clozapine,† cocaine, diazepam, donepezil, duloxetine, fluoxetine, fluphenazine, lamotrigine, meprobamate, methadone, methylphenidate, mirtazapine, naltrexone, nitrous oxide, olanzapine, pirenzepine, promethazine, quetiapine, risperidone/ paliperidone, rivastigmine, sertraline, TCAs, tranylcypromine, trazodone, trifluoperazine, valproate, venlafaxine, ziprasidone; may also be a feature of drugs causing hypersensitivity syndrome Agents associated with impaired platelet aggregation: chlordiazepoxide, citalopram, diazepam, fluoxetine, fluvoxamine, paroxetine, piracetam, sertraline, valproate Prothrombin time (PT)/international normalised ratio (INR) PT: 10–13 seconds INR: 0.8–1.2 Chloral hydrate, disulfiram, fluoxetine, fluvoxamine, mirtazapine, valproate; also agents interacting with warfarin Barbiturates, carbamazepine, phenytoin, tiotixene Red blood count F: 3.8–5.8×1012/L M: 4.5–6.5×1012/L Lithium, testosterone Buprenorphine, carbamazepine, chlordiazepoxide,

chlorpromazine, donepezil, haloperidol, meprobamate, phenytoin, quetiapine, trifluoperazine Red cell distribution width 11.5–14.5% Agents associated with anaemia, e.g. carbamazepine, chlordiazepoxide, citalopram, clonazepam, diazepam, lamotrigine, memantine, mirtazapine, sertraline, tranylcypromine, trazodone, valproate, venlafaxine None known Reticulocyte count 0.5–2.5% (or 50–100×109/L) None known Carbamazepine, chlordiazepoxide, chlorpromazine, meprobamate, phenytoin, trifluoperazine Agents associated with pure red cell aplasia: carbamazepine, clozapine, valproate *Previous reports of eosinophilia-myalgia syndrome may have been due to a contaminant from a single manufacturer. †May raise or lower levels. ‡Note that in rare cases clozapine has been associated with a ‘morning pseudo-neutropenia’ with lower levels of circulating neutrophil levels. As neutrophil counts may follow circadian rhythms, repeating the FBC at a later time of day may be instructive. F, female; M, male; MAOIs, monoamine oxidase inhibitors; TCAs, tricyclic antidepressants.

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