20 - Chapter 15 Miscellany

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.

02 - References

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03 - Summary of psychiatric adverse effects of non

Summary of psychiatric adverse effects of non-psychotropics

Miscellany CHAPTER 15 Summary of psychiatric adverse effects of non-psychotropics It is increasingly recognised that non-psychotropic medications can induce a wide range of psychiatric symptoms.1 Up to two-thirds of all drugs have potential psychiatric adverse effects listed in their product labelling,2 although in most cases the evidence supporting a causal link is limited. Psychiatric adverse effects are poorly characterised in drug clinical trials, often only becoming apparent during post-marketing surveillance.3 Given this level of uncertainty, suspected psychiatric adverse effects should be diagnosed and managed on a case-by-case basis. As a general guide, the psychiatric adverse effects of non-psychotropics are shown in Table 15.3. For individual drugs and agents not listed in this table, additional sources of information and the product literature should be consulted. Note that psychiatric adverse effects of drugs used in psychiatry and drugs for human immunodeficiency virus (HIV) and epilepsy are summarised elsewhere in this book. Table 15.3 Summary of psychiatric adverse drug reactions (ADRs) with non-psychotropics.4–7 Drug Psychiatric adverse effect Comment Analgesics Opioids Sedation, dysphoria, confusion, mood changes including euphoria, sleep disturbances, hallucinations, psychosis, delirium, dependence Psychiatric ADRs are relatively common with opioids. Psychosis during opioid withdrawal has also been reported rarely.8 5HT1 agonists (e.g. sumatriptan) Fatigue, anxiety, panic attacks Antibiotics Cephalosporins, penicillins, quinolones (including fluoroquinolones), tetracyclines Sleep disturbances (insomnia and somnolence, abnormal dreams, nightmares), anxiety, delirium and confusional states, depression and agitation, psychotic symptoms (e.g. hallucinations, suicidal ideation) All antibiotics can cause delirium. Patients with underlying medical conditions can be at higher risk of developing psychiatric ADRs. Of the quinolones, ciprofloxacin causes the most psychiatric ADRs, including mood disturbances, agitation and confusion. Onset of psychiatric ADRs can be fast, e.g. after one dose. Isoniazid9 Mania, psychosis Mood-elevating properties have long been noted. In rare cases has been associated with the emergence of manic/psychotic symptoms. Antimalarials Chloroquine, mefloquine Psychosis

including hallucinations, panic attacks, suicidal ideation and attempts, anxiety, depression, restlessness, confusion. Abnormal dreams/nightmares are common with mefloquine. Symptoms begin early in treatment. Patients should be advised to stop treatment if these develop and seek medical advice. Psychiatric ADRs are more common with mefloquine than chloroquine. Reactions can even occur after discontinuation of the drug. Mefloquine should not be prescribed for patients with an active or a history of a psychiatric diagnosis. (Continued)

970 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 15 Table 15.3 (Continued) Drug Psychiatric adverse effect Comment Antiparkinsonian treatments Levodopa Visual hallucinations, depression, hypomania, sleep disturbances, abnormal dreams, cognitive impairment, agitation, psychosis, delirium Dopamine agonists Sedation, psychomotor agitation, anxiety, akathisia, sleep disturbances, psychosis, cognitive impairment, delirium, visual hallucinations These are associated with more psychiatric adverse effects than levodopa Amantadine Decreased concentration, sleep disturbances, visual hallucinations, irritability, anxiety, depression, euphoria, fatigue, psychosis, delirium Selegiline (MAO-B inhibitor) Sleep disturbances, agitation, psychosis Primary metabolites include levamfetamines Entacapone (COMT inhibitor) Sleep disturbances, hallucinations, delirium Cardiovascular agents ACE inhibitors (e.g. captopril, lisinopril) Fatigue, hallucinations, delirium, mood disturbances Captopril most strongly associated with mood effects. Overall limited psychiatric ADRs. Beta-blockers Fatigue, sedation, sleep disturbances and nightmares, cognitive impairment, depression, hallucinations, psychosis, delirium Disturbances more common with lipophilic beta-blockers (e.g. propranolol, metoprolol) than with hydrophilic beta-blockers (e.g. atenolol, sotalol, nadolol). Propranolol most commonly associated with depressive symptoms, but even with this drug causality has not clearly been established. Reports of psychiatric ADRs from numerous clinical trials are equivocal. Calcium channel blockers (e.g. diltiazem, amlodipine) Mood changes, lethargy, dysphoria, mania, psychosis, delirium, akathisia Causal association not clearly demonstrated Statins10–12 (e.g. simvastatin, atorvastatin) Cognitive impairment, memory impairment, depression, emotional lability, irritability, sleep disturbance Causal associations between statins and changes in mood, sleep and cognition have not been established in systematic reviews of RCTs. Statins penetrate the blood–brain barrier; simvastatin has the highest permeability. Switching to hydrophilic statins (e.g. pravastatin, rosuvastatin) has been suggested in suspected cases of moderate to severe psychiatric ADRs.

Miscellany CHAPTER 15 Table 15.3 (Continued) Drug Psychiatric adverse effect Comment Corticosteroids Glucocorticoids (e.g. betamethasone, prednisolone, prednisone) Mood disorders, mania/ hypomania (particularly with higher doses),13 suicidal ideation, euphoria, agitation, sleep disturbances, psychosis and delirium, dementia, cognitive impairment Clear causal association. Most substantial associations are with depression and mania.14 Onset of psychiatric ADRs is often very sudden, and within the first 1–2 weeks of starting treatment. Symptoms generally respond to dose decreases and have been reported in association with several routes of administration (including oral, parenteral and inhaled), although are probably less common with inhalation. Symptoms usually resolve on gradual discontinuation, although duration of symptoms varies considerably. Other agents 5α-reductase inhibitors (e.g. finasteride)15 Depression, anxiety, suicidality A pharmacovigilance database study of finasteride found associations with suicidality and other psychological adverse events in younger patients receiving treatment for alopecia but not older patients receiving treatment for BPH.16 Chemotherapeutic agents (e.g. 5-fluorouracil, asparaginase, bortezomib, ifosfamide, vincristine) More commonly: cognitive impairment, delirium,

psychosis Less commonly: depression, anxiety, suicidal ideation Almost all chemotherapeutic agents are associated with significant psychiatric ADRs, which may be multifactorial in origin (i.e. secondary to the disease process, ADRs and psychological distress). Cancer therapy- associated cognitive changes include difficulty in executive functions, multitasking, short-term memory recall and attention. Cognitive changes seem to be dose- dependent, and certain drugs (methotrexate, fludarabine, cytarabine, 5-fluorouracil, cisplatin) are associated with worse cognitive effects. Cimetidine Cognitive impairment, delirium Interferons-α and -β Depression, loss of efficacy of previously effective antidepressants, suicidal ideation, delirium, non-specific psychiatric symptoms. Rare case reports of psychosis and mania with interferon-α. Psychiatric ADRs are relatively unlikely with interferon-β but much more widely reported with interferon-α. Interferon-α-associated depression responds to antidepressants, use of which can be preventative. Novel diagnostic biomarkers have been investigated to predict which patients are likely to develop interferon-α--associated psychiatric ADRs. (Continued)

04 - Differential diagnosis of psychiatric adverse

Differential diagnosis of psychiatric adverse effects

972 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 15 Differential diagnosis of psychiatric adverse effects A wide range of confounding factors complicate the diagnosis (and perhaps also the recognition) of psychiatric adverse effects. For example, physical illness, co--prescribed medication, non-prescribed agents and pre-existing mental illness may all influence the clinical presentation and outcome. Factors determining the probability of a causal relationship between drugs and psychiatric adverse effects are shown in Box 15.1. To further support clinical decision-making, the Naranjo scale can be used to assess the likelihood of any adverse reaction being drug-related (Table 15.4). Although cessation of the implicated non-psychotropic might be indicated in some cases, such decisions require individual considerations beyond the scope of this book. Table 15.3 (Continued) Drug Psychiatric adverse effect Comment Isotretinoin17 Depression, suicidal ideation, psychosis Sporadic reports of psychiatric ADRs but a causal link between isotretinoin therapy and depression, anxiety, mood changes or suicidal ideation/suicide has not been established. A recent meta-analysis found no epidemiological evidence to suggest an increased risk of suicide and psychiatric conditions with isotretinoin.18 Moreover, isotretinoin may be associated with a lower risk of suicide attempt following treatment.18 Rare, idiosyncratic reactions cannot be ruled out; if they occur the drug should be discontinued. Risk is no higher in those with prior suicide attempts and is not dose- or treatment-duration-related. Montelukast19 Sleep disorders, hallucinations, anxiety, depression, obsessive compulsive symptoms The UK MHRA has issued warnings about neuropsychiatric reactions associated with montelukast. Reactions have been reported in adults, adolescents and children. Evidence is conflicting, with one systematic review identifying associations with anxiety and sleeping disorders but not suicide and depression--related events.20 ACE, angiotensin-converting enzyme; BPH, benign prostatic hyperplasia; COMT, catechol-O-methyltransferase; 5HT, 5-hydroxytryptamine; MAO-B, monoamine oxidase B; MHRA, Medicines and Healthcare products Regulatory Agency; RCTs, randomised controlled trials.

Miscellany CHAPTER 15 Box 15.1 Factors determining the probability of a causal relationship between drugs and psychiatric adverse effects4,21 ■ ■Temporal relationship between the drug exposure and the psychiatric adverse effect ■ ■Evidence of the specific psychiatric adverse effect occurring with the suspected drug ■ ■Plausible pharmacological mechanism for the psychiatric adverse effect (e.g. dopamine agonists and psychosis) ■ ■Presence of alternative explanations for symptoms (e.g. pre-existing mental illness, de novo psychiatric illness, other drugs) ■ ■Response of symptoms to the withdrawal of the drug ■ ■Effect of rechallenge with the same drug Table 15.4 Adapted Naranjo adverse drug reaction (ADR) probability scale criteria.22 Questions Yes No NA/unknown

1. Are there previous conclusive reports on this reaction? +1 0
2. Did the ADR appear after the suspected drug was administered? +2 –1
3. Did the ADR improve when the drug was discontinued? +1 0
4. Did the ADR appear with rechallenge? +2 –1
5. Are there alternative causes for the ADR? –1 +2
6. Did the reaction appear when placebo was given? –1 +1
7. Was the drug detected in the blood at toxic levels? +1 0
8. Was the ADR more severe when the dose was increased, or less severe when the dose was decreased? +1 0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure? +1 0
10. Was the ADR confirmed by any objective evidence? +1 0 Probability score: ≥9 = definite; 5–8 = probable; 1–4 = possible; ≤0 = doubtful.

05 - References

References