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Chapter 22 Therapeutic issues Medication adherence Is adherence important? • It has been estimated that only one-third of patients prescribed medication actually adhere to the treatment plan (this applies to all medical specialties, not just psychiatry) and that 780% of psychiatric admissions relate to medication non-adherence. Adherence is a particular problem when the illness runs a chronic course and requires the patient to be on medication for life (e.g. diabetes, IHD, pulmonary disease, schizophrenia). • Patients with schizophrenia who comply with a sufficient dosage of antipsychotic medication have only about one-fifth the risk of relapse, compared to patients who do not take their medication.1 • There is good evidence that prophylactic lithium treatment of bipolar disorder reduces the likelihood of relapse (particularly manic relapse), as well as the risk of suicide.2 • Continuation of antidepressant treatment for at least 6mths after symptom resolution significantly reduces the risk of further depressive episodes.3 Reasons for non-adherence It is important to realize that the patient may have understandable reasons for being reluctant to take prescribed medication. Uncovering these reasons may help in negotiation and developing strategies to improve the situation. • Continued symptoms of the underlying disorder (e.g. delusions, lack of motivation, impaired insight, and disorganization) or comorbid disorders (e.g. substance misuse, personality disorder). • Negative attitude towards medication in general (vs other forms of treatment) or stigma associated with being ‘on medication’, particularly where there are external stigmata of treatment such as Parkinsonism (‘looking like a zombie’). • Unacceptable (or unexpected) side effects (e.g. weight gain, E Weight gain with psychiatric medication, p. 1000; sedation; EPSEs, E Antipsychotic-induced Parkinsonism, p. 1010; sexual dysfunction, E Sexual dysfunction and psychiatric medication, p. 1006; perceived loss of ‘good’ symptoms, e.g. hypomania). • Forgetting (genuine oversight, disorganization, cognitive impairment). • Lack of communication (reasons for medication not fully explained or understood). • Failure to obtain (or renew) prescription (through non-attendance, poor communication or poor relationship with responsible prescriber, e.g. GP). • Belief that the medication is ‘not working’. 1

National Institute for Health and Care Excellence (2014) Psychosis and schizophrenia in adults: pre vention and management. Clinical guideline [CG178]. M https://www.nice.org.uk/guidance/cg178 [accessed 12 July 2018]. 2 National Institute for Health and Care Excellence (2017) Bipolar disorder: assessment and man agement. Clinical guideline [CG185]. M https://www.nice.org.uk/guidance/cg185 [accessed 12 July 2018]. 3 National Institute for Health and Care Excellence (2009) Depression in adults: recognition and management. Clinical guideline [CG90]. M https://www.nice.org.uk/guidance/cg90 [accessed 12 July 2018].

Medication adherence • Feeling well and no longer seeing the need for medication. The 'reward' of freedom from side effects may be immediate, while the 'punishment' of relapse may be more distant, not taken seriously or not directly associated with stopping treatment. Strategies to improve adherence Education • Promote insight/understanding of the illness and benefits of treatment. • Provide information about the medication, how to take it, possible side effects, the length of time needed to see benefits, and the potential problems of suddenly stopping. • Discuss the reasons for prophylactic or continued treatment, especially when the patient feels well (e.g. to reduce the risk of relapse and improve long-term outcome). • Encourage discussion of pros and cons of suggested treatment plan. • Encourage openness about potentially embarrassing issues that may lead to non-adherence (e.g. sexual side effects). • Regularly ask about, and document, side effects at each review. Sensible prescribing • Simplify drug regime—use single dose where possible (most psychotropic medications have long half-lives and can be given once daily or are available in slow-release preparations). • Minimize side effects through choice of a medication with the lowest potential for side effects and using the lowest therapeutic dose. • If side effects are problematic, consider change to an alternative preparation or (where an alternative would be less effective) co- prescribing agents to counter significant problems. • Rationalize medication choice, based on individual acceptability of side effects (e.g. any weight gain may be unacceptable to a young ♀ patient). • Clear communication of any changes in regime both to the patient and primary care team (including written instructions for the patient and direct communication with the GP), especially if the primary care physician is the main prescriber. • Consider use of depot antipsychotic preparations—this may sometimes be requested by the patient but is more often necessary when the patient lacks insight or has had significant serious relapses related to non-adherence. • Regularly review the need for continued medication. Practical/behavioural measures • Written information to the patient, particularly where the regime is complex or where a change of dose/medication is planned. • Establish a regular daily routine for taking medication. • Use of a multicompartment compliance aid (e.g. Dosette® box). • Supervised administration (e.g. by relative/carer, at pharmacy, in day hospital, by CPN). • Active monitoring (e.g. tablet count; blood levels, E Plasma level monitoring, p. 998).

Chapter 22 Therapeutic issues Off-label prescribing Essence In the UK, licensed medicines are granted a Marketing Authorization (pre viously called a product licence) by the Medicines and Healthcare Products Regulatory Agency under the Human Medicines Regulations 2012. For each drug, the British National Formulary (BNF) specifies the doses, indications, cautions, and adverse effects, which reflect those in the manufacturer's Summary of Product Characteristics. However, in spite of various licensed treatments, patients will often remain symptomatic and psychiatrists will consider prescribing medications outside the narrow terms of their licence.4 Unlicensed prescribing does not imply lack of evidence in support of the proposed intervention and can still be safe and beneficial to the patient. In fact, it has also been argued that the product licence for a drug does

not necessarily represent the best use of that compound. General points • The real extent of unlicensed prescribing in the UK is largely unknown; however, a systematic review of antipsychotic prescribing in children, adults, and the elderly found that off-label prescribing can be found in up to 75% of prescriptions. • Drug companies do not usually test their medicines on children; hence, they cannot apply to license their medicines for use in the treatment of children. Nonetheless, BAP5 has stated that healthcare professionals have a responsibility to prescribe the most effective and safe treatments for the benefit of their patients, and practitioners should use their professional judgement to determine these uses. • No psychotropic medication is currently licensed for use in pregnancy or in breastfeeding mothers. • It has been argued that the final prescribing decision should rest with the clinician, based on the availability of other therapeutic options and careful assessment of the potential risks and benefits (see Box 22.1 for legal considerations). Types of unlicensed prescribing • The prescription of a medication for an indication that is not covered within the terms of the Market Authorization. • The prescription of a medication to a patient who lies outside the age range specified within the Summary of Product Characteristics. • The prescription of a medication at doses above the maximum recommended dosage (E Box 5.7 Guidelines for use of high-dose antipsychotics, p. 216). • The use of a licensed medication for longer periods than those specified within the Marketing Authorization. 4 Royal College of Psychiatrists (2017) Use of licensed medicines for unlicensed applications in psychi atric practice, 2nd edn (CR210 Dec 2017). M https://www.rcpsych.ac.uk/usefulresources/publica tions/collegereports/cr/cr210.aspx [accessed 9 July 2018]. 5 Sharma AN, Arango C, Coghill D, et al. (2016) BAP position statement: off-label prescribing of psychotropic medication to children and adolescents. J Psychopharm 30:416–21. M https://www. bap.org.uk/pdfs/BAP_Position_Statement_Off-label.pdf [accessed 9 July 2018].

Off-label prescribing Recommendations for unlicensed prescribing • Unlicensed prescribing should only occur when licensed treatments have been used or considered but excluded on clinical grounds (e.g. contraindications, risk of interactions). • The prescriber should be familiar with any possible benefits and risks of the proposed treatment (ask specialist pharmacist for further guidance). • Particular consideration is needed with children, older patients, and patients lacking capacity (E Consent to treatment, p. 936). • Whenever possible, a full explanation of the treatment should be given to the patient (and/or their relative, when relevant) and documented in the notes. • Whenever possible, agreement of the patient (and/or their relative, when relevant) should be obtained, but if not possible, this should be noted. • Prescription should be started cautiously, and the patient’s progress monitored closely, with full documentation of treatment effectiveness and tolerance. • If unsuccessful, treatment should be withdrawn carefully. Box 22.1 Legal principles applying to unlicensed prescribing • Legally unlicensed prescribing would not be held as a breach of the duty of care, as long as the prescriber had informed the patient of the risks that the patient would deem significant (Montgomery v Lanarkshire Health Board, 2015; E The Montgomery case, p. 937) • According to the case of Bolitho v City and Hackney Health Authority (1997), medical opinion should also be capable of withstanding logical analysis. In unlicensed prescribing, this implies that doctors consider the risks and benefits of varying treatment options, with due regard to the available evidence.

Chapter 22 Therapeutic issues Plasma level monitoring There are a limited number of drugs with well-established plasma levels that equate with efficacy. Plasma monitoring is a regular procedure only for lithium therapy. However, there may be a number of other reasons for requesting plasma

levels (bear in mind that assays for specific drugs may not be locally available and may need special arrangements). Many psychiatric drugs have marked variations in metabolism or large numbers of active me tabolites, making plasma levels difficult to interpret. Reasons for monitoring • Established therapeutic plasma levels (see Table 22.1). • Monitoring of any changes in plasma level that might affect efficacy (e.g. due to drug interactions, physical illness, pregnancy, or altered pharmacokinetics over time). • Clinical evidence of toxicity (e.g. lithium, anticonvulsants). • Where there is doubt about patient compliance (e.g. lack of effect despite adequate or even high-dose treatment). • In cases where the patient may be unable to report adverse effects (e.g. children, severe ID, dementia). • After OD, to confirm it is safe to restart medication. Plasma level monitoring of other psychotropics [aripiprazole (and dehydroaripiprazole), olanzapine, risperidone (and 9-hydroxy-risperidone), quetiapine, amisulpride, lamotrigine, sulpiride] is available in the UK6 and could be used in assessing adherence, dose optimization, and if acute poisoning is suspected. However, it is not advised in routine practice and other ways of establishing treatment adherence are preferred [e.g. measurement of serum prolactin (PRL) if the patient is on risperidone; E Hyperprolactinaemia with antipsychotics, p. 1004]. Table 22.1 Reference ranges for selected drugs Lithium (E Lithium, p. 350) 0.4–1mmol/L Valproate (E Valproate/valproic acid, p. 354) 50–100mg/L Carbamazepine (E Carbamazepine, p. 356) 4–12mg/L (>7mg/L may be more efficacious in bipolar disorder) Clozapine (E Clozapine 1: general guidelines, p. 218) 350–500mcg/L (0.35–0.5mg/L) 6 Viapath Laboratory, King’s College Hospital, London. M http://www.viapath.co.uk [accessed 9 July 2018].

Paradoxical reactions to benzodiazepines Paradoxical reactions to benzodiazepines Essence Paradoxical or ‘disinhibitory’ reactions to BDZs occur in a minority of pa tients (<1% of general population) and are characterized by acute excite ment and altered mental state:7 • i anxiety. • Vivid dreams. • Hyperactivity. • Sexual disinhibition. • Hostility and rage (‘aggressive dyscontrol’). Recognition is important, as behavioural disturbance may be exacerbated by inappropriate use of higher doses of BDZs. Note: similar types of reac tion are described for most CNS depressants (e.g. alcohol, barbiturates). Aetiology Not fully understood. Theories include: ‘release behaviour’ due to loss of frontal lobe inhibition through GABAA mechanism; BDZ-related reduction in 5-HT neurotransmission; BDZ-related reduction in ACh neurotransmission. Risk factors Children, learning disability, history of brain injury, dementia, BPD, antisocial personality disorder, history of aggression/poor impulse control, alco holism, family/personal history of paradoxical reaction, use of high-dose/ high-potency BDZs (e.g. alprazolam, clonazepam, flunitrazepam, triazolam), IV/intra-nasal administration. Management • Primary management is supportive. Nurse in a safe environment, with constant supervision. • Can use sedative antipsychotic to treat acute behavioural disturbance, if necessary. • In extreme cases, consider use of IV flumazenil (may require repeated doses). • Clearly record occurrence of paradoxical reaction, so future episodes of acute behavioural disturbance can be managed appropriately. 7 Paton C (2002) Benzodiazepines and disinhibition: a review. Psychiat Bull 26:460–2.

Chapter 22 Therapeutic issues Weight gain with psychiatric medication General points Weight gain is a significant cause of non-compliance with psychiatric medi cation, and patients often complain about increases in weight, even when clinicians may regard it as ‘clinically insignificant’. Effects on general health, self-esteem, and social embarrassment should not be overlooked. Antipsychotics Proposed mechanisms Sedation (reduced activity), thirst (anticholinergic side effects), reduced me tabolism, fluid retention, endocrine effects (i PRL, altered cortisol, altered insulin secretion),

increases in leptin levels (changes in ‘set-point’ weight), and altered neurotransmitters (e.g. 5-HT2C blockade, H1 histamine re ceptor blockade), genetic risk factors (e.g. HTR2C, MC4R genes) have all been proposed.8 Increased risk ♀, previous pattern of overeating, narcissistic traits, family or personal his tory of obesity. Effects of specific agents (See Table 22.2.) Management • Inform the patient about the risk of weight gain, and involve them in the choice of antipsychotic, if feasible. • Regular monitoring of weight. • Encourage a ‘healthy diet’, moderate physical exercise, and avoidance of high-calorie fluids. Involve a dietitian, if necessary. • Use the lowest therapeutic dose; introduce medication increases slowly; consider intermittent dosing. • Consider adjunctive prescribing (e.g. clozapine plus aripiprazole, to allow lowering of clozapine dose, augmenting with metformin, augmenting with betahistine ± reboxetine). Antidepressants Proposed mechanisms Reduced metabolism, carbohydrate craving (Note: may be a symptom of de pression itself), central serotonin mechanisms in regulating food intake (ap petite/satiety), H1 histamine receptor blockade (e.g. TCAs, mirtazapine). Effects of specific agents All antidepressants can cause weight changes (mostly gain); below are some of the more well-known associations. Weight gain Mirtazapine, mianserin, MAOIs, TCAs, citalopram, paroxetine. 8 Lett TA, Wallace TJ, Chowdhury NI, et al. (2012) Pharmacogenetics of antipsychotic-induced weight gain: review and clinical implications. Mol Psychiatry 17:242–66.

Weight gain with psychiatric medication Weight loss Bupropion, fluoxetine. Management • General advice about diet and exercise. Involve a dietitian, if necessary. • Use the lowest therapeutic dose. • Consider switching to an alternative antidepressant with a lower propensity for weight gain. • Adjunctive prescribing, e.g. naltrexone, ranitidine at night—may reduce ‘midnight snacks’, but rarely used clinically. Lithium9 Proposed mechanisms i intake of high-calorie drinks, hypothyroidism, i insulin secretion, oedema. Management Counselling and advice about diet and exercise, use of low-calorie drinks, low-salt diet. Other mood stabilizers • Carbamazepine—weight gain due to i appetite. • Valproate—weight gain which may be due to i serum leptin and insulin. • Gabapentin—marked weight gain in some cases (up to 10% above baseline weight). • Lamotrigine—not associated with weight gain, making it the ‘drug of choice’ for those who have experienced marked weight gain with other mood stabilizers. 9 Baptista T (1995) Lithium and body weight gain. Pharmacopsychiat 28:35–44. Table 22.2 Weight gain with antipsychotics* High risk Moderate risk Low risk Little association Clozapine Fluphenazine Haloperidol Aripiprazole Olanzapine Risperidone Amisulpride Chlorpromazine Paliperidone Sulpiride Quetiapine Trifluoperazine Ziprasidone Asenapine

- Source: data from Fenton WS (2000) Review: most antipsychotic drugs are associated with weight gain. Evidence Based Ment Hlth 3: 58.

Chapter 22 Therapeutic issues Antipsychotics and diabetes There is a general consensus that SGAs have a greater incidence in causing abnormalities in insulin sensitivity and diabetes (type 2), in comparison to FGAs. It is worth noting: • The aetiology of diabetes in a patient receiving antipsychotics may not be wholly attributable to the drug—many risk factors are shared with metabolic syndrome (see Box 22.2). • Patients with schizophrenia have a 2- to 3-fold higher risk of developing diabetes than the general population, even when drug use is controlled. • Psychiatrists ought not to initiate treatment of diabetes themselves without consulting the patient’s primary care physician and/or considering referral to a diabetes specialist. • Younger patients treated with antipsychotics may be at higher risk of developing diabetes than older adults. Pathophysiology Not

fully understood. Proposed mechanisms are: i visceral adiposity through histaminergic H1 antagonism, leptin resistance, i tumour necrosis factor (TNF)-α levels; inhibition of insulin secretion in pancreatic β-cells through antagonism of muscarinic M3 receptors; d glucose sensitivity through an tagonism of serotonergic 5-HT1A receptors; i insulin release through antag onism of adrenergic α2 receptors; inhibition of GLUT glucose transporter. Management • Prior to initiating antipsychotic treatment—determine baseline measures such as fasting glucose and HbA1c. • When a patient gains 5% or more of their initial weight—at any time during therapy, consideration should be given to switching to an antipsychotic with less weight gain liability (E Weight gain with psychiatric medication, p. 1000). However, it should be noted that weight gain can occur with all antipsychotics and considerable variability exists among patients receiving the same drug regarding the risk of metabolic effects. • For patients at risk of diabetes—changing to an antipsychotic less likely to cause metabolic effects should be balanced against the risks and benefits from continuing treatment with the same drug. Adjunctive treatments include oral hypoglycaemics (e.g. metformin) or insulin, and any metabolic abnormalities should be treated according to accepted national guidelines. • Lifestyle modifications—can be used successfully for weight control in highly motivated subjects and may be complementary to medication (i.e. calorie-controlled diet/regular physical exercise).

Antipsychotics and diabetes Box 22.2 Metabolic syndrome [syndrome X, insulin resistance syndrome, Reaven's syndrome, or CHAOS (Australia)] Essence Characterized by insulin resistance and abnormal adipose deposition and function. Associated with i risk of developing atherosclerotic disease (IHD and stroke), type 2 diabetes, fatty liver, and cancer. Affects a large number of people (up to 25% in some studies), and prevalence increases with age. Current guidelines allow diagnosis when at least three out of the following five criteria are present: • Fasting glucose: ≥100mg/dL (or receiving drug treatment for hyperglycaemia). • BP: ≥130/85mmHg (or receiving drug treatment for hypertension). • Triglycerides (TG): ≥150mg/dL (or receiving drug treatment for hypertriglyceridaemia). • High-density lipoprotein cholesterol (HDL-C): <40mg/dL in men or <50mg/dL in women (or receiving drugs for reduced HDL-C). • Waist circumference: ≥102cm in men or ≥88cm in women. If Asian ethnic group: ≥90cm in men or ≥80cm in women. Aetiology The cause of the metabolic syndrome is unknown. Debate surrounds whether obesity or insulin resistance is the cause of the metabolic syn drome or if they are consequences of a more far-reaching metabolic de rangement. A number of markers of systemic inflammation are often i, e.g. CRP, fibrinogen, interleukin-6, TNF-α. Proposed pathophysiology Development of visceral fat l i plasma levels of TNF-α (as well as adiponectin, resistin, PAI-1) l production of inflammatory cytokines and/or altered cell signalling l insulin resistance. Prevention Various strategies have been proposed. Usually include i physical activity (e.g. walking 30min every day) and a healthy, reduced-calorie diet. Treatment The first-line treatment is change of lifestyle (i.e. calorie restriction and physical activity). If drug treatment is required, the individual disorders that comprise the metabolic syndrome are treated separately: diuretics and ACE inhibitors for hypertension; and cholesterol-lowering drugs to lower low-density lipoprotein (LDL) cholesterol and TG levels and to raise HDL levels. Use of drugs that decrease insulin resistance, e.g. metformin and thiazolidinediones, is controversial and local guidelines will apply. Note: the term 'metabolic syndrome' dates back to at least the late 1950s but came into common usage in the late 1970s to describe various associations of risk factors with diabetes that had been noted as early as the 1920s. Confusion arose because the term was used by different authors to describe different, albeit related, syndromes, e.g. Haller (1997), Singer (1977), Phillips (1977, 1978). It was the eponymous

Gerald M Reaven who coined the term ‘syndrome X’ in his 1988 Banting lecture. He proposed insulin resistance as the underlying factor and did not include abdominal obesity as part of the condition. See: Reaven GM (1988) Diabetes 37:1595–607.

Chapter 22 Therapeutic issues Hyperprolactinaemia with antipsychotics Essence (See also Box 22.3.) Secretion of PRL by the pituitary is under inhibitory control via DA from the hypothalamus. Blockade of DA D2 receptors on the pituitary lactotroph cells by antipsychotics can raise PRL levels within minutes to hours of starting treatment. It occurs frequently with FGAs and some SGAs (risperidone, amisulpride) but is rare with other SGAs (olanzapine > quetiapine, clozapine, ziprasidone, aripiprazole). Clinical features Often asymptomatic but can include gynaecomastia, galactorrhoea, erectile dysfunction, loss of libido, and hypogonadism in men and oligo-/amenor rhoea, galactorrhoea, infertility, loss of libido, acne, hirsutism, and i risk of osteoporosis. Epidemiology Prevalence of hyperprolactinaemia with ‘PRL-raising’ antipsychotics is esti mated to be up to 50%, with greater prevalence in women. Risk factors ♀ sex (women of reproductive age are more at risk than post-menopausal women), postnatal period, children, and adolescents. Differential diagnosis Diseases of the pituitary (e.g. PRL-secreting pituitary adenomas) or hypo thalamus, severe primary hypothyroidism, liver cirrhosis, end-stage renal disease, acromegaly, stress, pregnancy, post-partum period, chronic co caine/marijuana use, opiates. Investigations • Measure PRL serum level: • When PRL-raising antipsychotics are used, it is helpful to obtain a pretreatment PRL level. • Secretion of PRL is pulsatile and may be raised in response to stress, meals, or post-ictally; hence, a blood sample must be taken 1hr after eating or waking. • Antipsychotics usually produce PRL elevation of up to six times the upper limit of the reference range. • Mild to moderate elevations should be checked with a second sample to exclude physiological surges. Box 22.3 Other drugs reported to cause hyperprolactinaemia • Antidepressants: modest elevation with serotonergic antidepressants, e.g. SSRIs, MAOIs, and some TCAs. • Dopamine-depleting agents: e.g. reserpine, tetrabenazine, methyldopa. • Other agents: e.g. metoclopramide, cimetidine, ranitidine, cyproheptadine, verapamil, atenolol, oestrogens, antiandrogens.

Hyperprolactinaemia with antipsychotics • Look out for signs of chest wall irritation (which can promote galactorrhoea and raise PRL) and signs of a sellar mass (e.g. headache, visual field defects). • Check TFTs (exclude hypothyroidism), creatinine/U&Es (exclude renal failure), and IGF-1 (exclude acromegaly). • If history of chronic alcohol misuse, check LFTs and perform abdominal examination to rule out hepatic cirrhosis. • If clinically suspected, do a pregnancy test. • If the patient is on oral antipsychotics and the aetiology remains uncertain, consider diagnostic short-term cessation of medication (72hrs usually suffices for serum PRL levels to fall to near-normal levels). • Consider CT/MRI and/or a referral to endocrinology. Management • Exclude other possible aetiologies. • Consider a change of medication to a PRL-sparing antipsychotic (e.g. clozapine, olanzapine, quetiapine, aripiprazole) or a reduction in dose if the patient’s mental state is stable (monitor closely). • Another option is augmentation with low-dose aripiprazole. • If problems persist or medication changes are precluded (or not tolerated), refer to endocrinology for consideration of other treatments: combined oral contraceptive (♀ only), DA agonists (amantadine, cabergoline, bromocriptine). • If the patient has been amenorrhoeic for ≥1yr, request bone mineral density (BMD) measurement in order to screen for osteoporosis. • Pre-menopausal women should be advised about resumption of normal menstrual cycle (and return of fertility) when changing antipsychotics, and use of contraception should be discussed. Note: asymptomatic

hyperprolactinaemia does not necessarily warrant (in itself) changes to medication.

Chapter 22 Therapeutic issues Sexual dysfunction and psychiatric medication The degree of sexual dysfunction experienced by patients taking psychiatric medication may be a major source of distress and a significant reason for non-adherence. Clinicians are notoriously poor at enquiring about these problems, despite reports that patients regard sexual side effects as the most troublesome of all medication-related problems. Pathophysiology Not fully understood, but the proposed pharmacological mechanisms of psychotropic-induced sexual dysfunction are as follows: • Libido—reduced by DA blockage and increase in PRL. • Arousal (erection or vaginal lubrication)—reduced by cholinergic blockade, DA blockage, α1-adrenergic blockade, and nitric oxide (NO) decrease. • Orgasm and ejaculation—inhibited by DA blockade, serotonin increase, α1-adrenergic blockade, and possibly PRL elevation. General points • Educate patients about possible sexual side effects, and routinely screen for any impairment of sexual performance. • Be able to distinguish between psychotropic-induced sexual dysfunction and those related to underlying psychiatric or medical conditions, other concurrent drugs, alcohol/substance misuse, environmental factors, and relationship difficulties. • Optimal treatment for sexual dysfunction requires a combination of pharmacological and psychological interventions. • Complaints of sexual dysfunction may suggest inadequate treatment of underlying mental illness. Antidepressants Sexual dysfunction is a possible adverse effect of all antidepressants, and all dimensions of sexual functioning can be affected. Clomipramine, SSRIs (paroxetine, sertraline, citalopram, fluoxetine), and venlafaxine appear to be most likely to cause sexual problems. Other TCAs show intermediate risk of dysfunction. Bupropion, moclobemide, and mirtazapine seem to have the lowest rates of sexual side effects. • Spontaneous remission occurs in 10% of patients, and partial remission in 11% of cases. • Dysfunction may be related to i serotonergic transmission, peripheral α1-adrenergic blockade, histaminergic antagonism, inhibition of NO, adrenergic/cholinergic imbalance. • Sexual side effects are likely to be dose-related. • Paroxetine is more likely to cause disorders of arousal and ejaculatory delay than other SSRIs. • Serotonergic antidepressants can also be employed in the treatment of premature ejaculation and paraphilias.

Sexual dysfunction and psychiatric medication Management • Watchful waiting to see if symptoms subside (less likely with SSRIs). • Reduce antidepressant to minimal effective dose. • Delay drug intake until after sexual activity. • Switch to another agent known to have fewer adverse sexual effects (e.g. mirtazapine, bupropion, nefazodone, moclobemide). • Adjunctive therapy (e.g. mirtazapine, buspirone, bupropion, sildenafil, cyproheptadine, amantadine). Antipsychotics The prevalence of sexual dysfunction associated with antipsychotics is 750%, with reports of problems in all groups of antipsychotic medication (usually reduced libido, impaired sexual arousal, orgasm difficulties, and ejaculation problems). • Dysfunction may be related to DA blockade, histaminergic antagonism, anticholinergic effects, hyperprolactinaemia (and a decrease in oestrogen and testosterone levels). • Sexual side effects appear to be dose-dependent. • 5-HT2A-blocking property of SGAs may reduce risk. • FGAs (especially thioridazine) and risperidone can affect all phases of sexual response. • Clozapine, quetiapine, and aripiprazole seem to have the lowest risk of sexual side effects. Management • Spontaneous remission may occasionally occur. • Dose reduction where possible. • Consider switching to a compound with fewer α1-blocking properties for ejaculatory/erectile disturbances or to a less anticholinergic drug for disorders of arousal. • Switching to a PRL-sparing antipsychotic (e.g. quetiapine, clozapine, aripiprazole) may improve several sexual side effects. • Adjunctive treatment with DA agonists (e.g. amantadine,

bromocriptine) may be tried, but evidence base is poor. • Consider use of phosphodiesterase inhibitor (e.g. sildenafil) for erectile dysfunction. Mood stabilizers • Lithium therapy—may impair desire and arousal but does not appear to have a major impact on patient self-satisfaction or subjective sense of pleasure during sexual activity. Although the occurrence of sexual dysfunction can be present in up to one-third of those taking lithium, it is usually mild and not a source of distress, and does not lead to non-compliance. • Carbamazepine and phenytoin—both increase PRL and decrease dehydroepiandrosterone and other adrenal androgen levels, making sexual dysfunction likely. Valproate is also associated with sexual dysfunction. • Lamotrigine—does not cause these changes and is associated with low likelihood of sexual dysfunction.

Chapter 22 Therapeutic issues Priapism Priapism10,11 is defined as a sustained, painful, involuntary erection that cannot be relieved by sexual intercourse or masturbation and that is unre lated to sexual desire. It can be classified into ischaemic (‘low flow’), arterial (‘high flow’), and stuttering, with the ischaemic variant being associated with

> 95% of cases. This most common variant is secondary to rigidity of the corpora cavernosa, with little or no arterial flow. Left untreated, erectile dysfunction is inevitable. As such, ischaemic priapism is a urological emer gency requiring immediate intervention. The single biggest predictor of out come is time to treatment. Clitoral priapism has also been reported and may be associated with either pain and discomfort or i libido and orgasmic response.12 Pathophysiology Ischaemic priapism is mostly idiopathic. However, proposed mechanisms include α1-adrenergic blockade and imbalance with cholinergic activity, re sulting in NO deficiency. Epidemiology Drug-induced priapism accounts for around a third of all cases of priapism. Differential diagnosis Haemotological disease (e.g. sickle-cell, thalassaemia, leukaemia), toxin- mediated infections (e.g. scorpion venom, spider bite, rabies, malaria), metabolic (e.g. amyloidosis), neurological (e.g. syphilis, CVA), malignancy (metastatic or regional infiltration), and medications (see Box 22.4). Investigations FBC, coagulation screen, penile blood gas analysis. 10 Salonia A, Eardley I, Giuliano F, et al. (2014) European Association of Urology guidelines on priapism. Eur Urol 65:480–9. 11 Priapus, the son of Zeus and Aphrodite, was a god with an enormous penis who symbolized the earth’s fertility. 12 Patel AG, Mukherji K, Lee A (1996) Priapism associated with psychotropic drugs. Br J Hosp Med 55:315–19. Box 22.4 Drugs reported to cause priapism • Antidepressants: trazodone, bupropion, fluoxetine, sertraline. • Antipsychotics: clozapine, risperidone, olanzapine, chlorpromazine, thioridazine, quetiapine, ziprasidone, aripiprazole, zuclopenthixol, haloperidol. • Other medications: sildenafil, antihypertensives (hydralazine, calcium channel blockers, propranolol), anticoagulants (heparin, warfarin), adrenergic α-blockers (prazosin, tamsulosin, terazosin), hormones (testosterone, GnRH, tamoxifen), metoclopramide, omeprazole, intraca-vernosal injection of vasoactive drugs. • Recreational drugs: alcohol, marijuana, cocaine.

Priapism Management • Always enquire about sexual side effects and history of prolonged erections (50% of patients presenting with priapism have a previous history of painless erections lasting for <1hr). • Counsel patients about the possibility of developing priapism, and educate them about the risks of leaving episodes of priapism untreated and the importance of seeking earlier treatment. • Avoid psychotropics with high α1-adrenergic antagonism (e.g. trazodone, sertraline, chlorpromazine, risperidone, ziprasidone) and polypharmacy with anticholinergic agents. • Immediate intervention should involve conservative measures such as pain control, vigorous hydration, and cold compresses. • First step in management is normally decompression by penile aspiration, followed by intracavernous injection of a sympathomimetic drug (phenylephrine). • If medical interventions fail or for priapism events lasting >72hrs, surgical care is warranted. This is in the form of shunt surgery. However, this surgery is generally not effective in preserving erectile function after 36hrs, so implantation of a penile prosthesis is recommended in such cases. • Recurrent 'stuttering' priapism can be managed with a trial of antiandrogens (only in patients who are fully sexually mature), oral β-agonists such as terbutaline, and a combination of prednisone and ketoconazole.

Chapter 22 Therapeutic issues Antipsychotic-induced Parkinsonism Essence A frequent adverse effect found in full form in at least 20% of patients treated with antipsychotic medication. Characterized by tremor, rigidity, and bradykinesia; the presentation is similar to that of idiopathic Parkinson's disease (E Parkinson's disease and related syndromes, p. 142); symp toms are always bilateral; tremor is more pronounced in action and pos ture, and there are other extra-pyramidal features such as akathisia. It is more common in elderly ♀ and in those with pre-existing brain damage. Generally occurs within 4wks of treatment, is dose-dependent and a major cause of non-compliance. Assessment Routine enquiry and clinical examination are generally sufficient to detect the onset of symptoms and should be carried out frequently in the first 3mths of treatment. Monitoring may help establish the minimally effective dose of antipsychotic needed by individual patients, reducing discomfort and improving compliance. Pathophysiology D2 receptor blockade in the nigrostriatal pathway. Differential diagnosis Many drugs have been associated with Parkinsonism (see Box 22.5), and some may increase the likelihood of problems (e.g. prednisolone). Other differentials include: idiopathic Parkinson's disease, dementia (e.g. DLB), negative symptoms of schizophrenia, and psychomotor retardation (e.g. in depression). Box 22.5 Other drugs reported to cause Parkinsonism • Antidepressants (e.g. SSRIs, MAOIs, TCAs). • Lithium. • Anticonvulsants (e.g. carbamazepine, valproate). • Analgesics (e.g. NSAIDs, opiates). • Drugs of abuse (e.g. cocaine, PCP). • Cardiovascular drugs (e.g. amiodarone, diazoxide, diltiazem, methyldopa, metirosine, nifedipine, tocainide). • GI drugs (e.g. cimetidine, domperidone, metoclopramide, prochlorperazine). • Anti-infection drugs (e.g. aciclovir, chloroquine). • Respiratory drugs (e.g. antihistamines, salbutamol, terbutaline). • Hormones (e.g. medroxyprogesterone). • Cytotoxics (e.g. ciclosporin, interferons). • Others (e.g. cyclizine, ondansetron, levodopa, tetrabenazine).

Antipsychotic-induced Parkinsonism Treatment Several strategies may be used, including: • Dose reduction. • Switching to another antipsychotic agent, most commonly second- generation, e.g. clozapine/quetiapine < olanzapine/aripiprazole < risperidone (<8mg/day). • Use of anticholinergic agents (e.g. procyclidine, orphenadrine, trihexyphenidyl) or amantadine (a DA agonist, so beware of potential worsening of psychosis). Of note, symptoms are usually absent during sleep, so night-time dose may not be required. Note: anticholinergic agents are often used in younger patients.

However, older patients may not be able to tolerate the side effects of blurred vision, dry mouth, constipation, urinary retention, and particularly cognitive im pairment. This has led to the use of amantadine, which is better tolerated, or more frequent use of the SGAs, especially when patients already have early signs of Parkinson's disease. Follow-up If anticholinergics are prescribed, the need for their continued use ought to be kept under review. Their slow withdrawal should be attempted after the acute phase of treatment or following any lowering of antipsychotic dose, as drug-induced Parkinsonism tends to resolve over time and additional medication may no longer be needed.

Chapter 22 Therapeutic issues Akathisia Essence Akathisia derives from the Greek meaning 'not to sit still' and de scribes an unpleasant, distressing side effect of antipsychotic treatment. Characteristically manifests with a subjective component—a feeling of inner restlessness (with the drive to engage in motor activity, especially involving the lower limbs and trunk) and an objective component—movements: such as pacing constantly; inability to stand, sit, or lie still; rocking; and crossing/ uncrossing legs. Subjective distress may dominate in the absence of any prominent motor phenomena. Clinical presentations • Acute akathisia—occurs within hours to weeks of commencing an antipsychotic or increasing its dose. • Acute persistent akathisia—is the chronic form of primary akathisia. • Tardive akathisia—usually develops after >3 months of treatment and can persist or worsen when antipsychotic medication is discontinued or reduced. Can be associated with less intense subjective restlessness and dyskinetic movements. Poorly responsive to anticholinergics. • Pseudoakathisia—may occur in older, ♂, schizophrenic patients with prominent negative symptoms and presents with overt motor restlessness without subjective distress. Pathophysiology Not yet fully understood, most likely due to imbalance of dopaminergic, noradrenergic and serotonergic mechanisms Risk factors (See Box 22.6.) Use of high-dose and/or high-potency antipsychotics, chronic use of antipsychotics, rapid increase/sudden withdrawal of antipsychotics, use of intramuscular depot preparations, history of organic brain disease (e.g. de mentia, alcoholism, HIV), history of previous akathisia, concomitant use of predisposing drugs (e.g. lithium, SSRIs). Differential diagnosis Anxiety/agitation (primary or secondary to other psychiatric disorders), drug withdrawal/discontinuation syndromes, acute confusional states, Box 22.6 Drugs reported to cause akathisia • Antipsychotics (usually high-potency): chlorpromazine (less likely), haloperidol, pipothiazine, prochlorperazine, promazine, thioridazine (less likely), trifluoperazine, zuclopenthixol, SGAs (risperidone/ ziprasidone/aripiprazole > olanzapine > quetiapine/clozapine). • Antidepressants: SSRIs duloxetine, venlafaxine, imipramine (and other TCAs). • Anxiolytics: alprazolam, buspirone, lorazepam. • Others: diltiazem, interferon alfa, levodopa, lithium, melatonin (withdrawal), metoclopramide, ondansetron, verapamil.

Akathisia encephalitis/meningitis, Parkinsonism/dystonia/TD, serotonergic syn drome (early symptoms), toxicity due to other drugs (e.g. recreational drugs—amphetamine, MDMA, cocaine; antidepressants; antihistamines; sympathomimetics; salicylate), RLS, iron deficiency anaemia, endocrine dis orders (e.g. thyrotoxicosis, hypo-/hyperglycaemia, phaeochromocytoma). Investigations FBC, LFTs, U&Es, glucose, TFTs, and urine drug screen. Management • Review history/medication to identify possible causative agent(s) and rule out any organic aetiology. • 0 Beware of akathisia possibly leading to increase/worsening of sucidality, violent behaviour, non-adherence to treatment, substance misuse, and long-term risk of TD. • If antipsychotic-related—treatment strategies are as follows. Change antipsychotic drug regimen • Reduce the dose of antipsychotic medication. • Try a low-potency FGA (e.g. chlorpromazine). • Switch to an

SGA with low akathisia potential (e.g. quetiapine). • Consider use of clozapine in cases of intractable akathisia. Add an anti-akathisia agent • Try β-blocker (propranolol 40–80mg/day) or low-dose mirtazapine (5- HT2A receptor antagonist) 15mg/day as first line. • Alternative option is mianserin (15mg/day) or cyproheptadine (8– 16mg/day) (both 5-HT2A receptor antagonists). • If the patient has concurrent Parkinsonism, consider use of anticholinergics (e.g. benzatropine, orphenadrine, procyclidine, trihexyphenidyl). • Consider BDZs (e.g. clonazepam, diazepam, lorazepam) alone or with propranolol, especially in chronic akathisia. • Amantadine (100mg/day) or clonidine (up to 150 mcg/day) may be tried if these treatments are ineffective. Course/prognosis Most cases will respond to treatment, usually after a few days. Chronic or tardive cases may be more difficult to treat, and therapeutic benefit (e.g. of propranolol) can take up to 3mths. Follow-up • Once akathisia has settled, keep any specific treatment under review. • Slow withdrawal of any additional agent should be attempted after a few weeks (in the case of BDZs) or after several months (for other agents). • If akathisia recurs, long-term therapy may be necessary. • The need for continued use of high-dose, high-potency antipsychotics should be reviewed in the light of any change in the clinical presentation of the primary psychiatric disorder.

Chapter 22 Therapeutic issues Tardive dyskinesia Essence Late onset (mean 7yrs), involuntary, repetitive, purposeless movements, occurring with long-term antipsychotic treatment (also reported in up to 10% of untreated schizophrenic patients). Patients are often unaware of the movements, which are first detected by friends and family members. Operational diagnostic criteria: ≥1 movement of moderate intensity or ≥2 movements of mild intensity after ≥3mths (1mth if >60yrs) of antipsychotic treatment or within 4wks (8wks for depot) of discontinuation. Symptoms/signs Peri-oral movements are the most common (e.g. tongue, lips, jaw), hence the alternative terms oral–lingual, orofacial, oro–bucco–facial, or buccal– lingual–masticatory dyskinesia. Other movements may include: axial— trunk twisting, torticollis, retrocollis, shoulder shrugging, pelvic thrusting; and limbs—rapid movements of the fingers or legs, hand clenching (and sometimes choreoathetoid movements). Symptoms can be consciously suppressed, worsen with distraction, are exacerbated by stress and anti- Parkinsonian agents, and disappear during sleep. Peripheral TD is more frequently associated with comorbid acute movement disorders (akathisia, tremor, Parkinsonism) than orofacial TD. Pathophysiology Not yet fully understood. Theories: striatal dopaminergic/cholinergic im balance, upregulation/supersensitivity of post-synaptic DA D2 receptors in the basal ganglia following chronic blockade, imbalance of D1/D2 receptors leading to striatal disinhibition of the thalamocortical pathway, and striatal GABA hypofunction leading to enhanced DA transmission. Epidemiology Prevalence is 15–30% of chronically treated patients but may be as high as 70% in ‘high-risk’ population, with 5% of patients per year of antipsychotic exposure developing TD. 750% of cases are reversible. Risk factors (See Box 22.7.) Chronic use of antipsychotics (especially in high dose), change/cessation of chronic treatment (especially intermittent treatment), concomitant anticholinergic treatment, elderly (>60yrs), ♀, organic disorder (e.g. dementia, ID, epilepsy), previous head injury, alcoholism, comorbid mood disorder, negative symptoms of schizophrenia, diabetes mellitus, his tory of previous drug-induced akathisia/Parkinsonism/dystonias, concomi tant use of predisposing drugs (e.g. lithium, antidepressants, stimulants). Differential diagnosis Stereotypies, tic disorders, other causes of dyskinesia (e.g. Parkinson’s disease or use of anti-Parkinsonian agents), hyperthyroidism (choreiform movements of the limbs), other causes of chorea/athetoid movements (e.g. Sydenham’s/Huntington’s chorea, WD), epilepsy. Investigations FBC, LFTs, U&Es, TFTs, Ca2+, serum copper, serum caeruloplasmin, anti- nuclear antibody (ANA),

antineutrophil cytoplasmic antibodies (ANCA).

Tardive dyskinesia Management • Review history/medication to identify possible causative agent(s). • Reduce the dose of such agent(s) to the minimum effective antipsychotic dose. Note: withdrawal of the offending antipsychotic may initially worsen TD. • Anticholinergic agents will exacerbate the problem and should also be slowly reduced and stopped, if possible. • If residual symptoms are tolerable, it is best to 'wait and see' before considering additional treatment, as TD tends to improve with time. • If residual symptoms are severe, interfere significantly with functional abilities, or may be life-threatening, consider an alternative antipsychotic—clozapine (reportedly effective in up to 43% of refractory cases), then quetiapine > olanzapine > risperidone. • Otherwise temporarily raising the dose of antipsychotic may give immediate relief, while addition of a specific treatment may be commenced (dose of antipsychotic should then be reduced again). Adjuvant agents • First line: tetrabenazine 25–200mg/day (beware its depressogenic effect). • DA agonists (e.g. low-dose bromocriptine 0.75–7.5mg/day, levodopa, amantadine). • BDZs (e.g. clonazepam), but evidence base is poor. • Calcium channel blockers. • Anticonvulsants (e.g. gabapentin, levetiracetam). • Antioxidants (e.g. vitamin E, though efficacy disputed). • Other (e.g. botulinum toxin, donepezil, amino acids, ondansetron, melatonin, pyridoxine, baclofen). • There is case report evidence for use of transcranial magnetic stimulation (TMS) (E Other physical treatments, p. 312). Course/prognosis Prevention is the best strategy, e.g. antipsychotic choice and close moni toring. Prognosis appears related to how soon the offending medication is discontinued. A balance needs to be struck between reduction in dyskinesia vs control of psychotic symptoms. Follow-up Closely monitor residual symptoms. Regularly review the need for con tinued antipsychotic treatment. Clearly record TD symptoms and the man agement plan in case notes. Box 22.7 Drugs reported to cause TD • Antipsychotics: phenothiazines, haloperidol, pimozide, rarely SGAs (quetiapine, olanzapine, amisulpride, risperidone, aripiprazole). • Other medications: anticholinergics, antidepressants (phenelzine, sertraline, fluoxetine, trazodone, amitriptyline, imipramine), anti-emetics (metoclopramide, prochlorperazine), antiepileptics (carbamazepine, phenytoin), antihistamines, lithium, amphetamines, methylphenidate, anti-Parkinson agents (bromocriptine, levodopa).

Chapter 22 Therapeutic issues Dystonic reactions Essence Syndrome of sustained, often painful muscular spasms, producing repeti tive, twisting movements, or abnormal postures that develop following ex posure to antipsychotic medication. Aetiology Remains unclear. Various mechanisms have been proposed such as alter ation in dopaminergic–cholinergic balance in the basal ganglia or, paradox ically, i nigrostriatal dopaminergic activity as a compensatory response to DAdopamine receptor blockade. Risk factors Previous/family history of dystonia, younger age group13 (rare in patients

> 45yrs), ♂ > ♀, liver failure, clinically severe schizophrenia (especially with marked negative symptoms), use of high-potency antipsychotics, hypocal caemia, recent cocaine misuse. Acute dystonia Usually occurs within 1wk of commencing or rapidly increasing the dose of the antipsychotic medication or of reducing the anticholinergic medication prescribed to treat it; 50% of cases occur within 48hrs, rising to 90% within 5 days of exposure. Incidence—710% of

> patients exposed to all antipsychotics (up to 30% with high-potency drugs). Symptoms/signs—muscles of the head and neck are most commonly affected with torticollis, trismus, jaw opening, forceful protrusion of the tongue, blepharospasm, grimacing, oculogyric spasm, and opisthotonus. The trunk and limbs are less commonly affected, and involvement of pha ryngeal and laryngeal muscles can cause serious symptoms such as dys phagia and laryngospasm. Usually more generalized in younger patients (may be confused with fits, especially in children) and more localized (head and neck) in older patients. Course—may fluctuate over hours, but most last minutes to hours without treatment. Tardive dystonia Develops days to months following exposure to DA receptor-blocking agents and does not improve rapidly with anticholinergic treatment. Incidence—1.5–4%. Symptoms/signs—similar to those seen in acute dystonia. It may present with a unique syndrome of retrocollis, opisthotonus, internal arm rotation, and elbow extension with wrist flexion. 13 Note: in contrast with most medication side effects, acute dystonias are more common in the young than the elderly. This may be related to asymptomatic loss of dopaminergic neurons in later life.

Dystonic reactions Course—tends to be chronic and symptoms can persist, even when offending medication is removed. Differential diagnosis—may resemble catatonia, tetany, TLE, malingering, conversion disorder, and hypocalcaemia. Management • If severe, discontinue suspected agent. • Emergency treatment with IM anticholinergic agents (e.g. procyclidine 5mg, benzatropine 2mg). IV administration is necessary only if dystonic reaction is life-threatening. • Continue use of anticholinergic prophylactically for 5–7 days, in addition to antipsychotic medication, and taper it off over 2–3wks (long-term treatment may predispose to TD). • Consider switching to antipsychotic with low propensity to cause EPSEs (see Box 22.8). • Alternative treatment includes use of amantadine (fewer side effects than other agents). • Oculogyric crisis that is unresponsive to anticholinergic drugs may benefit from treatment with clonazepam. • If treatment is unsuccessful, check serum Ca2+ concentrations in order to exclude hypocalcaemia. • Routine prophylaxis should be considered for patients with a history of previous drug-induced dystonic reaction. • TD may respond to botulinum toxin, ECT, and DBS (E Deep brain stimulation (DBS), p. 313). Box 22.8 Agents reported to cause dystonias • Antipsychotics: aripiprazole, clozapine (rare/abrupt withdrawal), flupentixol decanoate, haloperidol, olanzapine (rare), prochlorperazine, quetiapine, sulpiride, risperidone (rare), alimemazine, zuclopethixol. • Other psychotropics: benzatropine (rare), bupropion, buspirone, gabapentin, carbamazepine, cocaine (+ withdrawal), disulfiram (rare), mirtazapine, fluoxetine, midazolam, paroxetine, phenelzine, sertraline, TCAs. • Other (mostly rare/isolated cases): amiodarone, azapropazone, diphenhydramine, domperidone, ergotamine, indometacin, metoclopramide, nifedipine, penicillamine, prochlorperazine, promethazine, propranolol, sumatriptan.

Chapter 22 Therapeutic issues Neuroleptic malignant syndrome Essence A rare, life-threatening idiosyncratic reaction to antipsychotic (and other) medication (see Box 22.9), characterized by: fever, muscular rigidity, altered mental status, and autonomic dysfunction. Patients require acute medical services where intensive monitoring and treatment are available. Pathophysiology

Theories: secondary to DA activity in the CNS, i.e. striatum (rigidity) and hypothalamus (thermoregulation)—by blockade of D2 receptors or d DA availability; impaired Ca2+ mobilization in muscle cells, leading to rigidity (like malignant hyperthermia);14 sympathetic activation or dysfunction. Epidemiology Incidence 0.07–0.2% (pooled data); ♀:♂ = 2:1. Mortality 710%—deaths usually due to respiratory failure, cardiovascular collapse, myoglobinuric renal failure, sepsis, arrhythmias, thromboembolism, or dis seminated intravascular coagulation (DIC). Morbidity Rhabdomyolysis, aspiration pneumonia, renal failure, seizures, arrhythmias, DIC, respiratory failure, worsening of primary psychiatric disorder (due to withdrawal of antipsychotics). Symptoms/signs Hyperthermia (>38°C), muscular rigidity, confusion/agitation/altered level of consciousness, tachycardia, tachypnoea, hyper-/hypotension, diaphor esis/sialorrhoea, tremor, incontinence/retention/obstruction, creatinine kinase (CK)/urinary myoglobin, leucocytosis, metabolic acidosis. Box 22.9 Drugs reported to cause symptoms characteristic of NMS • Antipsychotics: aripiprazole, chlorpromazine, clozapine (rarely), flupentixol, fluphenazine, haloperidol, olanzapine, promazine, quetiapine (rarely), risperidone, thioridazine. • Anti-Parkinsonian agents: amantadine (+ withdrawal), anticholinergics (withdrawal), levodopa (+ withdrawal). • Antidepressants: amoxapine, clomipramine, desipramine, phenelzine, trimipramine, venlafaxine. • Other: carbamazepine (+ withdrawal), ganciclovir, ferrous sulfate, lithium, methylphenidate, metoclopramide, oral contraceptives. 14 A rare disorder associated with exposure to inhaled aesthetics and suxamethonium. Genetic linkage found to chromosome 19. Possibly due to a muscle membrane defect, leading to d intracel lular Ca2+ and intense muscle contractions. Temperature rises rapidly (up to 1°C/5min).

Neuroleptic malignant syndrome Risk factors i Ambient temperature; dehydration; patient agitation or catatonia; rapid antipsychotic initiation/dose escalation; withdrawal of anti-Parkinsonian medication; use of high-potency agents/depot IM preparations; history of organic brain disease (e.g. dementia, alcoholism), affective disorder, pre vious NMS; predisposing drugs (e.g. lithium, anticholinergic agents). Differential diagnosis Catatonia (E The catatonic patient, p. 1054); malignant hyperthermia;15 encephalitis/meningitis; heat exhaustion; Parkinsonism/acute dystonia; serotonergic syndrome; toxicity due to other drugs (e.g. amphetamine, MDMA, cocaine, antidepressants, antihistamines, sympathomimetics, sali cylates); DT; rhabdomyolysis; septic shock; haemorrhagic stroke; tetanus; phaeochromocytoma; strychnine poisoning. Investigations FBC, blood cultures, LFTs, U&Es, Ca2+ and phosphate levels, serum CK, urine myoglobin, ABGs, coagulation studies, serum/urine toxicology, CXR (if aspiration suspected), ECG; consider head CT (intracranial cause) and LP (to exclude meningitis). Management • Prompt diagnosis is vital. • Stop any agents thought to be causative (especially antipsychotics), or restart anti-Parkinsonian agents. • Consider appropriate care setting, e.g. ICU. • Supportive measures—oxygen, IV fluids, cooling (e.g. cooling blankets, antipyretics, cooled IV fluids, ice packs, evaporative cooling, ice water enema). To reduce the risk of rhabdomyolysis, also consider urinary alkalinization with IV sodium bicarbonate. • BDZs for acute behavioural disturbance or catatonia (E Severe behavioural disturbance, p. 1048). (Note: use of restraint and IM injection may complicate interpretation of serum CK.) • In cases not amenable to these measures, the following are often used, albeit with limited evidence base: dantrolene (IV 0.8–2.5mg/kg qds; PO 50–100mg bd), bromocriptine (PO 2.5–10mg tds, increase to max 60mg/day), amantidine (PO 100–200mg bd); nifedipine; consider ECT. (Note: i risk of fatal arrhythmias.) Course May last 5–7 days after stopping oral antipsychotics, and up to 21 days after depot antipsychotics (e.g. fluphenazine). Prognosis In the absence of rhabdomyolysis, renal failure, or aspiration pneumonia, and with good supportive care, prognosis

is good. 15 A rare disorder associated with exposure to inhaled aesthetics and suxamethonium. Genetic linkage found to chromosome 19. Possibly due to a muscle membrane defect, leading to d intracel lular Ca2+ and intense muscle contractions. Temperature rises rapidly (up to 1°C/5min).

Chapter 22 Therapeutic issues Follow-up Monitor closely for residual symptoms. Once symptoms have settled, allow 1–2wks (if possible) before restarting medication (use low-dose, low- potency, or atypical agents—avoid depot). Monitor patient, e.g. physical and biochemical parameters. Consider prophylaxis (bromocriptine). Inform the patient about the risk of recurrence if given antipsychotic medication. Ensure this is recorded prominently in their medical notes.

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Chapter 22 Therapeutic issues Serotonin syndrome Essence A rare, but potentially fatal, syndrome occurring in the context of initiation or dose increase of a serotonergic agent (other potential causes excluded, e.g. infection, metabolic, substance abuse, withdrawal, concurrent anti psychotic dose changes prior to symptom onset), characterized by altered mental state, agitation, tremor, shivering, diarrhoea, hyperreflexia, myo clonus, ataxia, and hyperthermia.16 Although SSRIs are commonly linked to SS, many other drugs (e.g. amphetaminess, MAOIs, TCAs, lithium) have the potential of causing hyperserotonergic symptoms. SS can occur as a result of OD, drug combinations (including OTC medications), and rarely with therapeutic doses. Pathophysiology Increase in circulating serotonin (5-HT) in the CNS. A variety of mechanisms can potentially increase the quantity or activity of serotonin: i production of serotonin due to i availability of precursors (L-tryptophan-containing substances); d metabolism of serotonin (MAOIs, selegiline); i release of stored serotonin (amphetamine, cocaine, fenfluramine, MDMA, meperi dine); reuptake inhibition [SSRIs, TCAs, SNRIs, noradrenaline and specific serotonin antagonists (NaSSAs), MDMA, dextromethorphan, meperidine, St John’s wort]; direct stimulation of serotonin receptors (buspirone, LSD); unknown mechanisms (lithium). Epidemiology Incidence is difficult to quantify, as mild cases probably go unreported. Mortality <1 in 1000 cases. Symptoms/signs • Psychiatric/neurological—confusion, nystagmus, agitation, seizures, coma. • Neuromuscular—myoclonus, rigidity, tremors (including shivering), hyperreflexia (usually lower, rather than upper, limbs), ataxia. • Autonomic—hyperthermia (may be secondary to prolonged seizure activity, rigidity, or muscular hyperactivity), GI upset (nausea, diarrhoea), mydriasis, tachycardia, hyper-/hypotension. Differential diagnosis NMS (see Table 22.3), malignant hyperthermia, infections (encephalitis/ meningitis, sepsis), metabolic disturbances, substance abuse (cocaine)/ withdrawal/OD (LSD, PCP). Investigations FBC, U&Es, LFTs, glucose, pH, biochemistry (including Ca2+, Mg2+, PO4, anion gap), CK, drug toxicology screen, CXR (if evidence of respiratory distress/possible aspiration), ECG monitoring (arrhythmia/conduction problems—prolonged QRS or QTc interval). 16 These are Sternbach’s diagnostic criteria; (Sternbach H (1991) The serotonin syndrome. Am J Psychiatry 148:705–13)—see also Dunkley EJC, Isbister GK, Sibbritt D, Dawson AH, Whyte IM (2003) The Hunter Serotonin Toxicity Criteria: simple and accurate diagnostic decision rules for serotonin toxicity. QJM 96:635–42.

Serotonin syndrome Treatment • Prevention with careful prescribing (E Table 6.3, p. 277) and patient education (e.g. with MAOIs, OTC medication) is pivotal • If severe, requires immediate transfer to the Emergency Department for supportive treatment and active management. • IV access—to allow volume correction (dehydration—insensible fluid loss due to hyperthermia) and

reduce the risk of rhabdomyolysis. • Rhabdomyolysis—should be dealt with quickly, with emphasis on maintaining a high urine output, combined with alkalinization using sodium bicarbonate. If necessary, reduce the temperature (e.g. cooling blankets, antipyretics, cooled IV fluids, ice packs, evaporative cooling, ice-water enema). • Pharmacotherapy—agitation, seizures, and muscular rigidity/myoclonus best managed using a BDZ [e.g. lorazepam IV (slow) 1–2mg every 30min; clonazepam]. Serotonin receptor antagonists may be considered in selected cases [e.g. cyproheptadine PO 4–8mg every 2–4hr (max 0.5mg/kg/day), chlorpromazine (risk of reduced seizure threshold), mirtazapine, methysergide, propranolol (mild 5-HT antagonist)]. Antihypertensives are usually unnecessary, unless hypertension is persistent and clinically significant (e.g. GTN IV 2mg/kg/min). Course and prognosis Onset is usually acute; however, recurrent mild symptoms may occur for weeks before the appearance of severe symptoms. Most cases resolve without sequelae within 24–36hrs with adequate supportive measures. Following an SSRI OD, a patient who remains asymptomatic for several hours is unlikely to need further medical management. Table 22.3 Distinguishing SS from NMS Although the clinical presentation of these two syndromes is very similar (i.e. autonomic dysfunction, alteration of mental status, rigidity, and hyperthermia), differentiation is very important as management may differ (e.g. use of chlorpromazine in SS, which may worsen NMS). Feature NMS SS Associated Rx Antipsychotics (idiosyncratic/ normal dose) Serotonergic agents (OD/drug combination) Onset Slow (days to weeks) Rapid Progression Slow (24–72hrs) Rapid Muscle rigidity Severe (‘lead pipe’) Less severe Activity Bradykinesia Hyperkinesia/clonus

Chapter 22 Therapeutic issues Antidepressant discontinuation syndrome Discontinuation symptoms can occur with all antidepressants17 and differ between antidepressant classes. However, they usually share three common features: abrupt onset within days of stopping the antidepressant, a short duration when untreated, and quick resolution when the original antidepressant is reintroduced. It is estimated at least a third of patients ex perience discontinuation symptoms. They are usually mild and self-limiting, but in a minority of cases, they can be severe and prolonged. Clinical features SSRIs and related discontinuation syndrome • Sensory symptoms—paraesthesiae, visual disturbance, shock-like sensations, and numbness. • Disequilibrium symptoms—most common: dizziness, vertigo, and light-headedness. • General somatic complaints—flu-like symptoms, fatigue, headache, sweating, and tremor. • GI symptoms—diarrhoea, vomiting, and nausea/vomiting. • Affective symptoms—irritability, anxiety/agitation, low mood, and tearfulness. • Sleep disturbance—nightmares, vivid dreams, and insomnia.18 TCA discontinuation syndrome Similar to SSRIs, but sensory and disequilibrium symptoms are less common with TCAs. MAOI discontinuation syndrome More severe than with other antidepressants and includes worsening of depressive symptoms, acute confusion, hallucinations, paranoid delusions, and anxiety symptoms with depersonalization. Uncommon clinical presentations Rare syndromes, such as mania/hypomania (E Box 7.2, p. 320), and Parkinsonian symptoms (see Box 22.5) may occur with all antidepressants. Course and duration Usually develops after 1mth of treatment, within 2–5 days after antidepres sant discontinuation or dose reduction. Onset of symptoms is unusual after

> “ 1wk. If untreated, duration is variable (1 day to 3wks). Resolution of symptoms usually occurs within 24hrs if antidepressant is reinstated. 17 The term

> ‘discontinuation’ is usually preferred to ‘withdrawal’ since the latter implies depend ence and there is no evidence antidepressants have a significant dependence liability according to internationally accepted criteria. 18 Haddad PM, Anderson IM (2007) Recognizing and managing antidepressant discontinuation symptoms. Adv Psychiat Treat 13:447–57.

Antidepressant discontinuation syndrome 1025 Aetiology Not completely understood. Various underlying mechanisms have been postulated such as acute decrease in synaptic serotonin in the face of downregulated or desensitized serotonin receptors, loss of inhibitory 5-HT tone on NA neurons, and cholinergic rebound. Risk factors Short half-life drugs (e.g. venlafaxine¸ paroxetine), duration of treatment ≤8wks (plateau in incidence afterwards), high dose stopped, anxiety symp toms at the start of treatment, previous history of discontinuation symp toms, young age. Differential diagnosis The diagnosis is generally a clinical one, but the Discontinuation-Emergent Signs and Symptoms (DESS) inventory can be used for evaluating SSRI dis continuation syndrome. Discontinuation symptoms can be misdiagnosed for: • Recurrence of depressive/anxiety symptoms. • Treatment ineffectiveness due to covert non-adherence. • Adverse reaction to new drug when switching across antidepressant classes. Other possibilities to be excluded are: • Underlying physical disorder. • Withdrawal from drugs of abuse/alcohol. • Mania/hypomania (timing of onset and symptoms such as dizziness and paraesthesiae strongly suggest ‘discontinuation mania’). Management • Tapering antidepressant is recommended to reduce the risk of developing discontinuation syndrome (use of liquid preparations may be helpful in allowing greater flexibility). However, guidelines on the optimum rates of dose reduction are at best empirical (E Table 6.3, p. 277), and a cautious approach is advised (over a 4-wk period if duration of treatment ≥8wks). • If mild to moderate and short-lived, symptoms can generally be tolerated by the patient, allowing successful discontinuation of antidepressant. • If severe, reintroduction of the original antidepressant rapidly resolves the symptoms. However, the syndrome may recur in up to 75% of patients when the same antidepressant is later discontinued. • Awareness of risk factors and symptoms of discontinuation syndrome and education of patients prior to stopping or tapering an antidepressant, should prevent unnecessary medical investigations. • Some symptoms of moderate severity can be treated symptomatically (e.g. hypnotic for insomnia, antimuscarinic agents for cholinergic rebound following TCA discontinuation). • For SSRI and SNRI discontinuation symptoms, another option is to switch to fluoxetine (due to its long elimination half-life). • If previous history of severe discontinuation symptoms and poor adherence to treatment, choice of antidepressant with low propensity to cause discontinuation symptoms (e.g. fluoxetine) should be considered.

Chapter 22 Therapeutic issues Hyponatraemia and antidepressants Essence Low serum Na+ (<135mmol/L) is a rare idiosyncratic side effect of all antidepressants, which may have serious consequences if undiagnosed. It is probably not dose-related, and its onset usually occurs within the first month of treatment. Aetiology Incompletely understood, but probably due to the syndrome of in appropriate secretion of antidiuretic hormone (SIADH), with resultant euvolaemic hypotonic hyponatraemia, possibly mediated by stimulation of serotonin and α1-adrenergic receptors. Risk factors Previous SIADH, history of hyponatraemia; low BMI, ♀ gender, age >80yrs; physical co-morbidity: diabetes mellitus, hypertension, head injury, hypo thyroidism, renal impairment, heart

disease, hepatic impairment, COPD, al coholism; other medications (e.g. thiazides > loop diuretics, calcium channel blockers, chemotherapy, NSAIDs, carbamazepine). Antidepressants • Current use of any antidepressant is associated with an i risk of hypona traemia.19,20 • SSRIs are associated with the highest risk. • The association with TCAs and SNRIs is slightly lower. • NaSSAs carry the lowest risk, with mianserin the only antidepressant not to carry such a risk. Clinical features Depend upon the severity, duration, and rate of change in serum Na+. May be asymptomatic or display symptoms and signs ranging from nausea, muscle cramps/weakness, and malaise to hypertension, lethargy, confusion, and, if severe, seizures and coma. Investigations Check renal, hepatic, cardiac, thyroid, and adrenal function; volume status; serum lipids and protein (to exclude pseudohyponatraemia); serum glucose (raised in hypertonic hyponatraemia); urine osmolality (>100mOsm/L in dicates impaired free water excretion); serum osmolality; urinary Na+ con centration (usually >20–40mmol/L with SIADH). Differential diagnosis • Psychogenic polydipsia. • Severe malnutrition. 19 Leth-Møller KB, Hansen AH, Torstensson M, et al. (2016) Antidepressants and the risk of hyponatremia: a Danish register-based population study. BMJ Open 6:e011200. 20 De Picker L, Van Den Eede F, Dumont G, et al. (2014) Antidepressants and the risk of hyponatremia: a class-by-class review of literature. Psychosomatics 55:536–47.

Hyponatraemia and antidepressants • Antipsychotic-induced (water intoxication, SIADH, severe hyperlipidaemia/hyperglycaemia). • Cirrhosis; alcoholism. • Nephrotic syndrome; heart failure. • Malignancy, e.g. lung (small-cell), pancreas, prostate, lymphoma. • CNS disorders, e.g. meningoencephalitis, abscess, stroke, subarachnoid/ subdural haemorrhage, head injury, Guillain–Barré, vasculitis. • Respiratory disorders, e.g. TB, pneumonia, abscess, aspergillosis. • Endocrine/metabolic disease, e.g. severe hypothyroidism, hypoadrenalism, pituitary insufficiency, porphyria. • Drugs, e.g. opiates, chlorpropamide, cytotoxic agents, diuretics, carbamazepine, NSAIDs, MDMA. Management Prevention—baseline U&Es prior to commencing antidepressant, with moni toring for those at high risk (at 2 and 4wks, then every 3mths). Treatment • If serum Na+ is <125mmol/L: refer to specialist medical care, and withdraw offending agent immediately. • If serum Na+ is >125mmol/L: continue to monitor U&Es daily until

> 135mmol/L. • Consider a lower-risk antidepressant (e.g. mirtazapine) or, if treatment urgent, ECT may be an option. • Consider fluid restriction and/or careful use of demeclocycline under specialist advice. • If necessary, rechallenge may be possible without recurrence (low dose, gradual increase, close monitoring).

Chapter 22 Therapeutic issues Prescribing in pregnancy Data are limited (and often conflicting) regarding the safety of psychotropic drugs in pregnancy. Some have been associated with i risks of birth defects or neonatal adverse events. Untreated mental illness during pregnancy is also an independent risk factor for major congenital malformations (MCMs) or obstetric complications (see Box 22.10). The most up-to-date summary of evidence is on the UK Teratology Information Service website (M http://www. uktis.org/) [accessed 11 July 2018]. Antipsychotics • Based on the available evidence, no definitive association has been found between in utero antipsychotic exposure and an i rate of MCMs and abnormal postnatal development. • FGAs are usually considered to have minimal teratogenic potential. • For SGAs, most evidence is with olanzapine, clozapine (i rate of

gestational diabetes, but no i risk of MCMs), and quetiapine (lowest placental passage, no evidence of an i rate of MCMs.) • Depot formulations and anticholinergic drugs should be avoided. Box 22.10 Guiding principles For all women of childbearing age • Always consider (and ask about) the possibility of pregnancy. • Pregnancy test recommended before starting any teratogenic drug. • Counsel the patient about the necessity of adequate contraception. • Advise further consultation if pregnancy is planned. For a planned conception • Discuss risks/benefits of discontinuation/continuation of medication (relapse vs teratogenicity, time to conceive, no decision risk-free). • Avoidance of all drugs during the first trimester (maximum teratogenic potential is between wks 2 and 9) is ideal, but often not achievable. In pregnancy • Theoretically, drugs that cross the blood–brain barrier can cross the placental barrier. • Consider switching to a lower-risk drug, if possible, use the lowest viable dose, avoid polypharmacy, and monitor closely. • Pregnancy may alter the pharmacokinetics of drugs, hence dosages may need to be adjusted (e.g. lithium). • Gradual withdrawal of some drugs (e.g. BDZs, TCAs, SSRIs) prior to delivery may help avoid 'withdrawal' effects in the newborn baby. Unexpected pregnancy • If >9wks, no urgent decision needed as major risk period has passed. • Consider reducing dose, if possible, and prescribe nutritional supplements (e.g. folic acid). • Do not stop lithium abruptly, and use caution with some SSRIs. • Valproate and carbamazepine should be avoided.

Prescribing in pregnancy Antidepressants • Untreated affective illness in pregnant women may be associated with an i risk of pre-term delivery, low birthweight, and poorer long-term developmental outcomes. • TCAs and SSRIs do not seem to be major teratogens but can cause neonatal withdrawals (agitation, irritability) if used in the third trimester. • Among TCAs, nortriptyline is recommended since it is less anticholinergic and hypotensive than amitriptyline and imipramine. • SSRIs (most experience with fluoxetine; less safe is paroxetine) may be associated with low birthweight, spontaneous abortion, and, if used in the third trimester, neonatal pulmonary hypertension. Sertraline appears to have the lowest placental passage. • MAOIs and other antidepressants should be avoided. Anxiolytics • Neonatal respiratory depression, hypothermia, hypotonia ('floppy baby syndrome'), and withdrawal syndromes may occur when BDZs are used close to delivery. • High doses and use in the first trimester increase the teratogenic risk. • There may be an association between first-trimester exposure to BDZs (especially diazepam) and an i risk of facial clefts. • Short-term use and minimum effective dose are recommended if BDZs are necessary. Promethazine is often preferred but should be avoided in the last 2wks of pregnancy. • Low-dose chlorpromazine or amitriptyline can be used, if necessary. Mood stabilizers • All commonly used mood stabilizers are teratogenic and contraindicated in women of childbearing age. Mood-stabilizing antipsychotic therapy is a preferable alternative. • Lithium (E Lithium, p. 350) has been associated with a 1:1000 risk of Ebstein's anomaly of the tricuspid valve, and detailed ultrasound/ echocardiography is indicated at 16–18wks. Relapse rates on discontinuation (50% within 2–10wks) usually preclude stopping lithium therapy in pregnancy. Serum monitoring, dose adjustment, and adequate hydration are essential (particularly after delivery). NICE guidelines state that lithium levels should be monitored every 4wks until 36wks, and weekly until delivery. Delivery in hospital is advised, and lithium should be stopped during labour. Neonatal problems include 'floppy baby syndrome', non-toxic goitre, hypothyroidism, nephrogenic diabetes insipidus, and cardiac arrhythmias. All neonates exposed to lithium in utero should have their serum lithium levels measured shortly after delivery. • Valproate and, to a lesser extent, carbamazepine are associated with neural tube defects (hence folic acid supplementation is recommended, although evidence for benefit is inconclusive). Valproate has been associated with i risk of long-term

cognitive deficits and craniofacial, cardiac, or limb defects. • Lamotrigine is associated with i rate of cleft palate.

Chapter 22 Therapeutic issues Prescribing in lactation 0 Absolute contraindications Psychotropic drugs should be avoided if the infant is premature or suffers from renal, hepatic, cardiac, or neurological disorders. General points • All psychotropic medications should be regarded as passing into breast milk (to a greater or lesser degree). A review of up-to-date evidence should be undertaken by clinicians prior to prescribing.21,22 • The benefits of breastfeeding to the mother and infant must be carefully weighed against the risks of neonatal exposure to drugs. • Of the limited studies examining this problem, the general findings are that levels of most psychotropic drugs in breast milk are relatively low and infant serum levels (ILs) may be undetectable. • Although infant exposure may be relatively low from breast milk (much lower than in utero exposure if the mother was taking medication during pregnancy), there is a risk of both withdrawal symptoms and adverse effects on development. • Evidence may be lacking for specific risks; nonetheless, caution should be exercised. • Monitoring of the infant should include biochemical (renal and liver function tests) and behavioural measures, with the involvement of a paediatrician to ensure development is within normal parameters. Choice of medication in nursing mothers • Where possible, consider non-pharmacological treatments. • If medication is necessary, the lowest effective therapeutic dose should be used and polypharmacy should be avoided. • Unless otherwise contraindicated, consider continuing with the psychotropic used during pregnancy in order to minimize any withdrawal effects in the newborn. • Avoid the use of drugs which are sedating and with long half-lives. Antipsychotics • Limited data preclude any conclusive prediction on the long-term safety of the available antipsychotics in lactation. • Among FGAs, most evidence is with haloperidol and chlorpromazine and has not shown any clear adverse infant effects. • A few case reports indicate low breast milk levels with risperidone, quetiapine, and olanzapine. 21 McAllister-Williams RH, Baldwin DS, Cantwell R, et al. (2017) British Association for Psychopharmacology consensus guidance on the use of psychotropic medication preconception, in pregnancy and postpartum 2017. J Psychopharmacol 31:519–52. M https://www.bap.org.uk/pdfs/BAP_Guidelines-Perinatal.pdf [accessed 12 July 2018]. 22 National Institute for Health and Care Excellence (2014, updated 2017) Antenatal and postnatal mental health: clinical management and service guidance. Clinical guideline [CG192]. M https://www. nice.org.uk/guidance/cg192 [accessed 12 July 2018].

Prescribing in lactation • There is one case report of cardiomegaly, jaundice, and sedation with olanzapine, but this finding may be spurious. • Clozapine should not be used, as there is a risk of agranulocytosis and seizures in the infant. Antidepressants • Available evidence is reassuring with regard to the safety of SSRI use in lactating women, with few reports of adverse effects on exposed infants. • Low ILs have been found with all SSRIs, but higher concentrations have been reported with fluoxetine and citalopram, which should therefore be used with caution. • Sertraline should be considered first line. Paroxetine may also be used. Low ILs and no adverse effects in the nursing infant are also reported with TCAs, with imipramine and nortriptyline being recommended as drugs of choice. • Limited data are available on other antidepressants. Anxiolytics • BDZs are excreted in breast milk and have lower infant milk/plasma ratios than other psychotropic medications. • Adverse effects such as sedation, lethargy, and weight loss have been reported with the use of BDZs. • BDZs with a short half-life, such as lorazepam, are preferable to longer- acting ones (e.g. diazepam). Mood stabilizers • Valproate and carbamazepine are regarded as compatible with

breastfeeding. However, some adverse effects have been noted; hence, close monitoring of the infant is advised. Moreover, they should be avoided in women of childbearing age. • Previous case reports found high ILs and adverse infant effects (such as cyanosis, hypotonia, heart murmur, lethargy) being associated with lithium. • However, recent data have shown no serious adverse event and relatively low ILs. • Infants may be more susceptible to dehydration and lithium toxicity, owing to immature renal function. It is not recommended. • Lamotrigine is not recommended due to theoretical risk of life- threatening Stevens–Johnson syndrome. Strategies to minimize infant exposure • Breastfeeding should be avoided at the time when serum levels in the mother are likely to be at their peak (check drug information for these values). • If possible, medication should be given as a single dose before the infant's longest sleep period. • Breastfeeding should occur immediately before taking the next due dose. • Alternatively, breast milk may be expressed when serum levels are at their lowest. Moreover, the first few millilitres can be expressed and discarded prior to breastfeeding.

Chapter 22 Therapeutic issues Prescribing for patients with cardiovascular disease General points In considering a suitable psychotropic drug, the main issues revolve around the propensity of that drug to interact with other medications the patient may be taking to affect BP or lead to cardiac conduction problems (see Box 22.11). Due to the unpredictability of drug interactions, polypharmacy is best avoided. Box 22.11 The QTc question Awareness of QT prolongation, as measured by the corrected QT interval (QTc), has been heightened because of the potential (but rela tively rare) risk of fatal arrhythmias (e.g. torsades de pointes). QTc is derived by dividing the QT interval by the square root of the cycle length, i.e.: QTc = QT (R -R) Normal QTc is 380–420ms; >440ms for men and >470ms for women— some concern; if >500ms—'at risk'. Causes of prolonged QT interval Acute myocardial ischaemia, myocarditis, bradycardia (e.g. atrioven tricular block), head injury, hypothermia, electrolyte imbalance (K+ d, Ca2+ d, Mg2+ d), congenital, sotalol, antihistamines, macrolides (e.g. erythromycin), amiodarone, antipsychotics (especially phenothiazines), antidepressants (especially TCAs). General advice Good practice dictates use of routine ECG prior to commencement of antipsychotic medication (especially pimozide, thioridazine, and other phenothiazines) or other psychotropics with known cardiac side effects (e.g. fluvoxamine, citalopram/escitalopram), and regular monitoring. Management QTc 440–500ms (men), 470–500ms (women): • Repeat ECG. • Review current medications and any potentially offending agents. • Consider dose reduction of any agents suspected of prolonging QTc. QTc >500ms: • Stop potential offending drug. • Switch to an alternative with lower effect, e.g. aripiprazole if an antipsychotic is needed; sertraline if SSRI is required. • Refer to a cardiologist.

Prescribing for patients with cardiovascular disease Specific contraindications BDZs and clomethiazole in pulmonary insufficiency; disulfiram and lithium in heart failure or sick sinus syndrome; lofexidine in post-MI patients. Pimozide is best avoided in most conditions. Myocardial infarction • Antidepressants—best avoided in the first 2mths; if clinically indicated, SSRIs (sertraline is the drug of choice), rather than TCAs (but avoiding fluvoxamine and citalopram/escitalopram). If sedation is required, consider use of mirtazapine or a small dose of trazodone at night. • Antipsychotics—high doses should be avoided; phenothiazines are generally more hypotensive than butyrophenones; clozapine should be used with caution in the first year post-MI; of the newer antipsychotics, olanzapine may offer the best risk–benefit balance. Heart failure Where possible, hypotensive agents (β-blockers, clozapine, risperidone, TCAs) and drugs causing fluid retention (carbamazepine, lithium) should be avoided. Angina/ischaemic

heart disease Avoid hypotensive agents and those known to cause tachycardia (pheno thiazines, clozapine, risperidone). Hypertension Avoid agents that may raise BP (MAOIs, low-dose TCAs, phenothiazines, clozapine, high-dose venlafaxine). Arrhythmias (See Box 22.11.) • Antidepressants—SSRIs should be first choice (but not fluvoxamine or citalopram/escitalopram). • Antipsychotics—high doses should be avoided; if essential, options with little to no effect on QTc include aripiprazole, olanzapine, sulpiride, and risperidone.

Chapter 22 Therapeutic issues Prescribing for patients with liver disease General points • Almost all psychotropic drugs are metabolized by the liver. • Exceptions to this rule include lithium, gabapentin, sulpiride, and amisulpride, which have minimal (or no) liver metabolism. • Most drugs are highly protein-bound (with the exception of citalopram, escitalopram, sulpiride, and amisulpride), and plasma levels may be i in liver disease. • In liver disease, when using drugs with high first-pass clearance (e.g. imipramine, amitriptyline, desipramine, doxepin, haloperidol), initial doses should be low. • Where possible, phenothiazines (e.g. chlorpromazine), hydrazine, and MAOIs (may be hepatotoxic) should be avoided. • Avoid drugs that are very sedative and constipating (anticholinergic) due to i risk of precipitating hepatic encephalopathy. • LFTs can be a poor marker of hepatic metabolic impairment; hence, always consider the clinical presentation too. Risk factors For drug-induced hepatotoxicity, risk factors include: older age, alcohol in take, ♀ sex, obesity, genetic vulnerability, and concomitant prescription of enzyme-inducing drugs. Antidepressants • Always start with the lowest possible dose, and titrate slowly. • TCAs—best evidence for use of imipramine; avoid amitriptyline, dothiepin, and lofepramine (most hepatotoxic). • SSRIs—some evidence for paroxetine and citalopram; avoid sertraline. Also i risk of bleeding with all SSRIs. • MAOIs—best avoided. • Others—venlafaxine (use 50% of usual dose), mirtazapine (cautious use), reboxetine (extensively metabolized, very low starting dose), trazodone (highly protein-bound, so low starting dose; avoid in severe impairment). Agomelatine (avoid). Antipsychotics • Best evidence for low-dose haloperidol (considered ‘drug of choice’), followed by sulpiride or amisulpride. • Clozapine dose should be kept low (some evidence of hepatotoxicity). Avoid in symptomatic or progressive liver disease. • Aripiprazole should be used cautiously, especially in severe disease. • Olanzapine (up to 7.5mg) may be safe (but does induce transaminases). • Risperidone doses should be kept low (half doses) • Quetiapine is extensively metabolized (hence, start low—25mg).

Prescribing for patients with liver disease Mood stabilizers • Lithium is the ‘drug of choice’, with gabapentin as second choice. • Valproate is contraindicated in severe liver disease but may be used with caution in mild to moderate impairment. • Caution should also be exercised with carbamazepine and lamotrigine, with metabolism impaired in severe disease. Anxiolytics • Where necessary, use low doses of short-acting BDZs (e.g. lorazepam, oxazepam, temazepam). • A low dose of zopiclone 3.75mg can be used with care in moderate hepatic impairment.

Chapter 22 Therapeutic issues

Prescribing for patients with renal impairment General points • Renal impairment generally leads to accumulation of drugs (or active metabolites) that are predominantly cleared by the kidney. This will lead to higher serum levels and i risk of dose-related side effects (e.g. postural hypotension, sedation, EPSEs). • Hence, all

psychotropics should be started at a low (or divided) dose, i slowly, and carefully monitored (for efficacy and tolerability). • When patients are receiving dialysis, seek specific advice from the manufacturer—dosages should usually be reduced by at least 50% and dosing separated in time from dialysis itself. Classification of chronic kidney disease

See Box 22.12 for estimation of glomerular filtration rate (GFR). CKD may be classified as mild (GFR 60–89mL/min), moderate (GFR 30–59mL/min), severe (GFR 15–29mL/min), or end-stage (GFR <15mL/min). Box 22.12 Estimating glomerular filtration rate (GFR) GFR Normal value 7125mL/min; it is the volume of fluid filtered by the glom eruli per minute

(mL/min) and can be directly measured by collection of urine over 24hr or estimated in adults in two ways: • Creatinine clearance (CrCl)—using the Cockcroft–Gault equation: CrCl mL /min F 140 age in yrs ideal body weight kg [ ] ( ) ( ) ( ) ( )

× / serum creatinine mol/L μ( ) F 1.23 men and 1.04 women

( ) ( ) CrCl is not accurate in conditions where plasma creatinine is unstable (pregnancy, children, diseases raising creatinine plasma level) and in se vere renal failure. • Estimated GFR (eGFR)—using the Modification of Diet in Renal Disease (MDRD) formula. It gives an eGFR for a 1.73m2 body surface area (if the body surface area is more or less than 1.73m2, then eGFR is less accurate). eGFR (mL/min/1.73m2) = 175 × {[serum creatinine (µmol/L)/84.4]–1.154} × age (yrs)–0.203 × 0.742 if ♀ × 1.21 if African-American or African-Caribbean Online calculator is available at: M http://www.renal.org/eGFRcalc/ GFR Note: most current drug dose recommendations are based on the CrCl estimations from Cockcroft and Gault. However, the most widely used method for estimating GFR is the MDRD equation, as this has proved the most robust and accurate.

Prescribing for patients with renal impairment Antidepressants • In severe renal failure, avoid duloxetine, fluoxetine, venlafaxine, and lofepramine (unless the patient is on dialysis). • Otherwise cautious use, beginning low and gradually increasing the dose is advised. • No specific therapeutic dose adjustments are necessary for MAOIs (except for isocarboxazid), RIMAs, mianserin, tryptophan, trazodone, or TCAs. Antipsychotics • Lower doses are recommended to avoid dose-related side effects (particularly with phenothiazines, which may be best avoided). • Highly anticholinergic agents should be avoided due to risk of urinary retention. • Clozapine is contraindicated in severe renal impairment. • Avoid amisulpride/sulpiride (primarily renally excreted), and use caution with risperidone. • Some authorities recommend haloperidol, but accumulation is possible, so careful monitoring is still necessary. Mood stabilizers • Lithium should be used with caution in mild to moderate impairment, with regular serum lithium monitoring. Avoid in severe impairment. No specific problems are reported for valproate or carbamazepine, although in severe renal failure, serum levels should be monitored. • Gabapentin requires specific dose adjustments, and manufacturer’s recommendations should be sought. • Lamotrigine should be used cautiously, particularly in severe renal impairment. Anxiolytics/hypnotics • BDZs tend to accumulate, with increasing CNS side effects (particularly sedation)—hence use low doses and those with a shorter half-life, e.g. lorazepam. • Buspirone is contraindicated in moderate to severe renal failure. • β-blockers should be started at low dose, as they may complicate renal failure by reducing renal blood flow. • Zopiclone and zaleplon require no dosage adjustment. However, the half-life of zolpidem may be doubled in renal failure, so it should be avoided. Others • Anticholinergics, disulfiram—use cautiously. • Acamprosate—contraindicated if serum creatinine >120µmol/L. • Anticholinesterases—no reported problems. Avoid galantamine in severe renal impairment.

Chapter 22 Therapeutic issues Prescribing for patients with epilepsy General points (See also E Psychiatric aspects of epilepsy 1, p. 138.) In considering a suitable psychotropic, there are two related considerations: • The propensity of that drug to interact with other medications the patient may be taking (justifying serum monitoring where possible). • Risk of lowering the seizure threshold and exacerbating the condition. As these effects appear dose-related, daily dose of any drug should be kept as low as possible. Greater caution is necessary when: • Other psychotropics are also being given (e.g. regular plus ‘as required’ antipsychotics). • Patients may be withdrawing from CNS depressants (e.g. BDZs, barbiturates, or alcohol). Risk factors Risk factors for psychotropic-induced seizures include: history of epilepsy, old age, polypharmacy, reduced drug clearance, pre-existing EEG abnor malities, cerebral arteriosclerosis, neurological impairment. Antidepressants • All TCAs appear to lower the seizure threshold, although there appears to be

greater risk with amitriptyline, clomipramine, and dothiepin. • Tetracyclics (maprotiline and amoxapine) also appear pro-convulsant, as does bupropion. • The other antidepressants appear less likely to cause problems, and a usual first choice is often an SSRI (may be anticonvulsant at therapeutic doses). Antipsychotics • The greatest risk of seizures is associated with the use of phenothiazines (especially chlorpromazine) and particularly clozapine. Because of this risk, it is quite common to cover high doses of clozapine with concomitant use of valproate. Hence, greater caution is needed when clozapine is used in individuals with epilepsy. • Olanzapine has been associated with seizure activity. • Avoid depot antipsychotics. • The lowest risk is associated with haloperidol (best choice), sulpiride, trifluoperazine, zuclopenthixol, amisulpiride, pimozide, quetiapine, risperidone, and aripiprazole. Mood stabilizers • Lithium does cause seizures in OD. However, a therapeutic dose has a low pro-convulsive effect. • If in doubt, anticonvulsants provide useful alternatives. However, clinical efficacy must be weighed against any potential risks of using lithium.

Prescribing for patients with epilepsy Anxiolytics/hypnotics • Generally these drugs are anticonvulsant. • Exceptions include buspirone, zolpidem, and β-blockers, although there is no evidence that they are epileptogenic. Others • Anticholinergics, acamprosate—no problems reported. • Disulfiram—caution is recommended. • Anticholinesterases—care is needed with donepezil and rivastigmine; however, galantamine appears safe.

Chapter 22 Therapeutic issues Physical health monitoring and antipsychotics General points All patients prescribed antipsychotics should have their physical health, as well as mental health, regularly monitored. This is not only due to the fact that some antipsychotic medications can have cardiometabolic adverse ef fects as previously outlined, but also that patients with schizophrenia have a significantly lower life expectancy and can be less prone to seek medical help. Below is an amalgamation of current physical health monitoring guide lines suggested by SIGN23 and NICE.24 Baseline • Essential—weight and waist circumference, pulse, BP, fasting blood glucose, HbA1c, blood lipids, nutritional status, smoking status, diet and physical activity levels, ECG. • If clinically indicated—serum PRL. 1 month • Essential—weight and waist circumference. • If clinically indicated—pulse, BP, fasting blood glucose, HbA1c, blood lipids, serum PRL, ECG (particularly if physical examination identifies cardiovascular risk factors, there is a personal history of cardiovascular disease, or the patient is being admitted as an inpatient). 3 months • Essential—weight and waist circumference, pulse, BP, fasting blood glucose, HbA1c, blood lipids, smoking status. • If clinically indicated—serum PRL, ECG. 1 year • Essential—weight and waist circumference, pulse, BP, fasting blood glucose, HbA1c, blood lipids, nutritional status, smoking status, diet, and physical activity levels. • If clinically indicated—serum PRL, ECG. This monitoring should continue annually thereafter, unless there is a change in antipsychotic prescription or physical health status. If any ab normalities are found, they should be treated in line with current guide lines (e.g. dietitian input, smoking cessation, treatment of diabetes, hypercholesterolaemia, etc.). 23 Scottish Intercollegiate Guidelines Network (2013) Management of schizophrenia. SIGN 131. M http://www.sign.ac.uk/assets/sign131.pdf [accessed 11 July 2018]. 24 National Institute for Health and Care Excellence (2015) Psychosis and schizophrenia in adults. Quality statement 6 ‘Assessing physical health’. Quality standard [QS80]. M https://www.nice.org.uk/guidance/qs80/chapter/quality-statement-6-assessing-physical-health#source-guidance-6 [accessed 11 July 2018].