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MPP202T Pharmacotherapeutics II, M.Pharm Semester 2

Unit 2: Psychiatric Disorders and Renal System

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2.1 Schizophrenia

Schizophrenia is a chronic psychotic disorder characterised by distortions of thought, perception, emotion and behaviour in clear consciousness, with onset typically in late adolescence or early adult life and a course of acute episodes over a background of persisting functional impairment in many patients. Its aetiology is neurodevelopmental and multifactorial: strong genetic contribution, prenatal and perinatal adversity, and environmental risks including cannabis use in adolescence, urban upbringing, migration and childhood trauma, converging on abnormal brain development and connectivity. Its pharmacology rests on the dopamine hypothesis in its modern form: excess dopaminergic activity in mesolimbic pathways driving the positive symptoms, and deficient dopaminergic function in prefrontal cortex contributing the negative and cognitive symptoms, with glutamatergic and serotonergic dysfunction woven into current accounts; the hypothesis is incomplete, but every established antipsychotic acts on dopamine receptors, which is why it still organises teaching. Symptoms divide for examination into positive symptoms, delusions, hallucinations most characteristically auditory, formal thought disorder and disorganised behaviour, added to normal experience; negative symptoms, flat affect, poverty of speech, anhedonia, avolition and social withdrawal, subtracted from it and the stronger predictor of poor function; and cognitive symptoms of attention, working memory and executive function. Diagnosis is clinical, from the characteristic symptoms sustained over time with functional decline, after exclusion of organic causes and substance induced states of Section 2.5, and its differential includes the mood disorders with psychosis of the next section.

Pharmacotherapy is antipsychotic therapy, and its classes divide by generation with a trade of harms that must be stated plainly. First generation or typical antipsychotics block dopamine D2 receptors strongly and control positive symptoms reliably, at the cost of extrapyramidal effects, acute dystonia, parkinsonism indistinguishable from Section 1.3 except by its drug cause, akathisia, and with chronic use tardive dyskinesia, together with prolactin elevation and its sexual, menstrual and bone consequences. Second generation or atypical antipsychotics combine D2 blockade with serotonin receptor antagonism and carry lower extrapyramidal liability, at the cost of metabolic harm, weight gain, diabetes and lipid disturbance most marked with some agents, sedation, and agent specific cautions such as the blood monitoring programme that clozapine demands for agranulocytosis. Clozapine alone holds proven efficacy in treatment resistant schizophrenia, defined by failure of adequate trials of other antipsychotics, and is reserved to specialist service with mandatory monitoring for that reason. Long acting injectable preparations answer the central practical problem of the illness, covert non adherence and relapse, and are offered as a positive choice, not a punishment. Management is a programme, not a prescription: acute episodes treated with an antipsychotic chosen on previous response and tolerability, maintenance therapy continued because relapse prevention is its strongest evidence, anticholinergic medicines only for established extrapyramidal effects and reviewed, metabolic monitoring as routine, psychological therapy and family intervention alongside, smoking and substance use addressed, and physical health owned jointly, since cardiovascular disease, not suicide alone, is the large cause of the shortened life of this population.

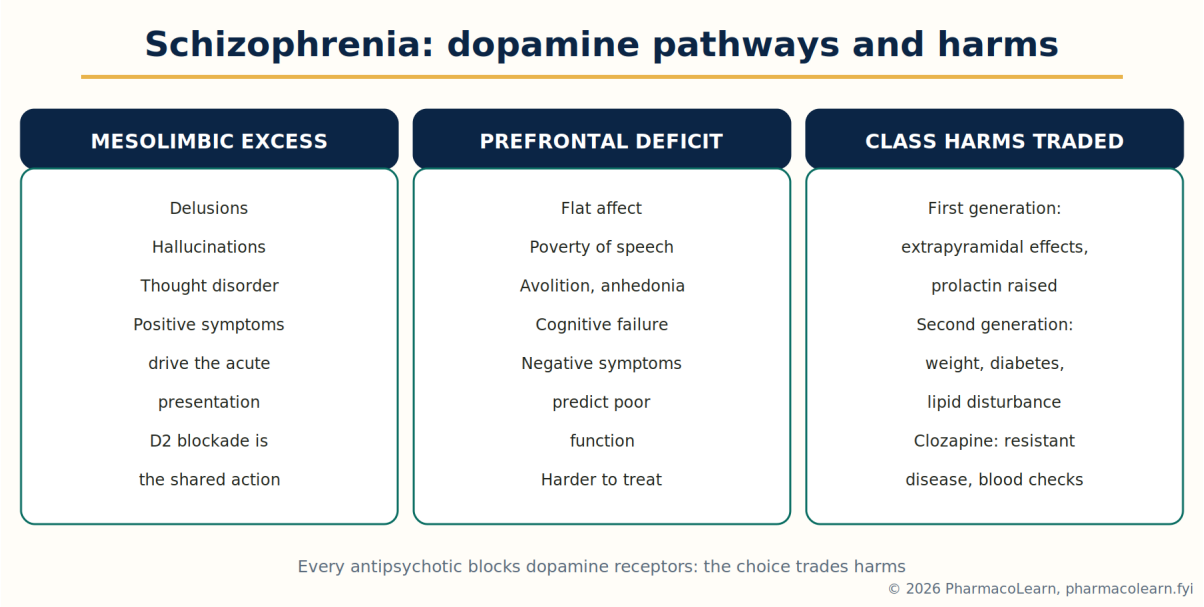

Figure: Dopamine in two directions. Positive and negative symptoms sit in different pathways, and class choice trades harms.

2.2 Depression

Depression, major depressive disorder in the formal name, is a mood disorder defined by persistent low mood or loss of interest and pleasure, anhedonia, sustained over weeks with a cluster of accompanying symptoms and functional impairment, distinguished from ordinary sadness by duration, pervasiveness and that impairment. Its aetiology is biopsychosocial: genetic vulnerability, early adversity and current stress, personality and medical illness, hypothyroidism and chronic disease among them, and medicines of Section 2.5, converging on disturbed monoamine neurotransmission, serotonin, noradrenaline and dopamine, stress axis overactivity and impaired neuroplasticity; the monoamine account is the framework the drug classes are built on, presented in modern teaching as a partial explanation rather than the whole disease. Presentation combines psychological symptoms, low mood, anhedonia, guilt and worthlessness, poor concentration and thoughts of death and suicide, with somatic symptoms, disturbed sleep with early waking, appetite and weight change, loss of energy and libido and unexplained aches; psychotic depression adds mood congruent delusions and hallucinations and is a severity marker demanding combined treatment. Diagnosis is clinical, graded by severity and symptom count, with suicide risk assessed directly and without embarrassment at every presentation, bipolar disorder excluded by a history of mania or hypomania before antidepressant therapy is started, because antidepressants can destabilise untreated bipolar illness, and physical causes and substance use reviewed.

Pharmacotherapy is one arm of a stepped programme in which psychological therapy holds an equal place, talking therapies first or alongside in milder illness and combined treatment in moderate to severe disease. The antidepressant classes are matched to patient factors more than to efficacy differences, since their average efficacy is similar and their harm profiles differ. Selective serotonin reuptake inhibitors are the usual first line class: effective, comparatively safe in overdose and generally tolerated, with early nausea and activation, sexual dysfunction, hyponatraemia in older patients and discontinuation symptoms on abrupt stopping as their teaching cautions, and the serotonin syndrome of Section 2.5 as their dangerous interaction. Serotonin and noradrenaline reuptake inhibitors add noradrenergic action, serve pain syndromes of Section 1.7 as well, and carry blood pressure and discontinuation cautions. Tricyclic antidepressants are effective older agents limited by anticholinergic burden, cardiac conduction effects and lethality in overdose, reserved accordingly. Monoamine oxidase inhibitors are specialist agents whose dietary tyramine and drug interaction discipline is a classical examination topic. Mirtazapine serves where sedation and appetite stimulation are wanted and sexual effects are to be avoided; other agents, including

the melatonergic and multimodal drugs, fill defined niches. Treatment is continued for a sustained period after remission because early stopping is the commonest cause of relapse, response is reviewed over weeks not days, switching, augmentation and combination are specialist stepped options in resistant depression, and electroconvulsive therapy remains the most effective treatment for severe, psychotic or life threatening depression. The pharmacist contribution is adherence through the delayed onset, which patients abandon in the gap between side effects arriving and benefit following, interaction vigilance for serotonergic and QT prolonging combinations, and direct enquiry about suicidal thinking where concern exists.

2.3 Anxiety disorders

The anxiety disorders are a family of conditions in which anxiety, the anticipatory response to perceived threat, becomes excessive, persistent and disabling: generalised anxiety disorder, free floating worry across many domains with muscle tension, restlessness, poor concentration and disturbed sleep; panic disorder, recurrent unexpected panic attacks of intense fear with palpitations, breathlessness, chest pain and fear of dying, followed by avoidance; phobias, specific and social, fear cued by defined objects or scrutiny; obsessive compulsive disorder, intrusive unwanted thoughts and the compulsive rituals performed to neutralise them; and post traumatic stress disorder, re experiencing, avoidance and hyperarousal after trauma. Their aetiology blends genetic and temperamental vulnerability, early experience, and dysregulation of the fear circuitry centred on the amygdala with serotonergic and noradrenergic modulation, the transmitter systems the drug classes address. Presentation overlaps heavily with physical disease, palpitations suggesting cardiac disease, breathlessness respiratory disease, and the diagnostic work is double: recognise the anxiety pattern and exclude the physical mimics, thyrotoxicosis of Part I, phaeochromocytoma and substance and caffeine effects among them, without endless reinvestigation that itself feeds the anxiety. Diagnosis is by the characteristic pattern and duration for each disorder, graded by severity and avoidance, since avoidance is the mechanism by which anxiety disorders shrink a life.

Pharmacotherapy is again one arm of care, cognitive behavioural therapy being the psychological treatment with the strongest evidence across the family and the first offer in phobias and obsessive compulsive disorder. Selective serotonin reuptake inhibitors are the first line drug class across generalised anxiety, panic disorder and obsessive compulsive disorder, with serotonin and noradrenaline reuptake inhibitors as the alternative class, both requiring the same patience and discontinuation care as in depression, and obsessive compulsive disorder characteristically needing longer and more determined trials. Benzodiazepines enhance GABAergic inhibition and relieve anxiety rapidly, and their place is deliberately narrow: short term use in crisis and severe acute symptoms only, because tolerance, dependence, withdrawal seizures on abrupt cessation, falls and cognitive harm in older people, and interference with psychological therapy all argue against maintenance use; the prescribing discipline of this class, agreed duration, no repeat without review, gradual reduction in established users, is a standing pharmacist duty. Buspirone serves generalised anxiety without dependence liability but with slow onset. Beta blockers serve performance anxiety by blocking its peripheral adrenergic symptoms and treat no core anxiety disorder. Pregabalin, licensed for generalised anxiety in some settings, carries its own dependence caution. Sleep, caffeine, alcohol self medication and the benzodiazepine like hypnotics of the next section are reviewed in every plan.

2.4 Sleep disorders

Sleep disorders present to pharmacotherapeutics chiefly as insomnia, difficulty initiating or maintaining sleep or early waking with daytime consequence, sustained beyond an acute disturbance and not explained by inadequate opportunity for sleep. Insomnia is classified by its company: primary insomnia as a conditioned hyperarousal disorder, perpetuated by worry about sleep and by compensating behaviours that

entrench it, and secondary insomnia riding on depression and anxiety of the preceding sections, pain of Section 1.7, respiratory and cardiac disease, restless legs, sleep apnoea, and the medicine list itself, stimulants, corticosteroids, beta blockers and decongestants among the culprits. Obstructive sleep apnoea, repeated upper airway collapse in sleep with snoring, witnessed pauses and unrefreshing sleep and daytime sleepiness, is the sleep disorder with the largest physical consequences, cardiovascular and metabolic, and its treatment is mechanical, continuous positive airway pressure, with weight management, not hypnotic; a hypnotic prescribed into undiagnosed apnoea worsens the night it was meant to mend. Diagnosis of insomnia is a sleep history and diary, screening for apnoea, mood and medical causes, and review of substances including caffeine, alcohol and nicotine, whose evening use fragments the sleep their users then medicate.

Pharmacotherapy of insomnia begins with its non drug core, which is also its most effective long term treatment: sleep hygiene education and cognitive behavioural therapy for insomnia, stimulus control and sleep restriction among its techniques, offered before or alongside any hypnotic. Hypnotic medicines are short term, lowest exposure, reviewed support for acute and severe insomnia, not a maintenance strategy: the benzodiazepine hypnotics and the related Z drugs acting at the same receptor complex, zolpidem, zopiclone and their relatives, shorten sleep latency at the cost of tolerance, dependence, rebound insomnia on stopping, falls and fractures and next day impairment in older patients most of all. Melatonin and its receptor agonists serve defined niches, circadian disorders and older patients in some guidance. Sedating antihistamines and sedative antidepressants used off this indication carry anticholinergic and next day burdens that limit them. The pharmacist pattern across the unit repeats deliberately: in anxiety and sleep alike, the sedative classes relieve tonight and mortgage tomorrow, and the professional skill is holding their use short, tapered and reviewed while the durable treatments take hold.

2.5 Drug induced psychiatric disorders

Medicines disturb mind as reliably as they disturb lung, liver and blood in Part I, and this head collects the patterns an examination expects to be recognised from a drug timeline. Drug induced psychosis and mania follow dopaminergic and stimulant exposure: corticosteroids, whose psychiatric effects range from euphoria and insomnia through mania to psychosis and depression on withdrawal and are the commonest inpatient culprit; dopaminergic therapy of Section 1.3 producing hallucinations and delusions in Parkinson disease; stimulants including amphetamines and cocaine producing a paranoid psychosis mimicking schizophrenia; cannabis and the synthetic cannabinoids; and withdrawal states, delirium tremens of alcohol withdrawal at their head. Drug induced depression is reported with corticosteroids again, with interferon based therapy classically, with some hormonal and cardiovascular agents in older teaching whose evidence is now read more cautiously, and the examination discipline is to weigh the association honestly rather than recite lists. Serotonin syndrome is the dangerous serotonergic excess state: agitation, confusion, hyperthermia, sweating, tremor, hyperreflexia and clonus following initiation, increase or combination of serotonergic medicines, selective serotonin reuptake inhibitors with monoamine oxidase inhibitors, tramadol, triptans or linezolid among the combinations, and it is a medical emergency treated by stopping every serotonergic agent, supportive and cooling care and specialist therapy. Neuroleptic malignant syndrome is its dopaminergic mirror: rigidity, hyperthermia, autonomic instability and altered consciousness after dopamine blockade or abrupt dopaminergic withdrawal, treated by stopping the blocker, supportive critical care and specific therapy under specialist direction. The extrapyramidal and metabolic harms of Section 2.1, anticholinergic delirium in older patients from the accumulated burden of bladder, bowel, eye and sleep medicines, and benzodiazepine and Z drug dependence complete the survey. Management across all patterns is one sequence: suspect the drug from the timeline, stop or reduce the culprit where safe, treat the syndrome supportively and specifically, document and report the reaction, and rebuild the prescription without the cause, because the commonest error in this topic is treating a drug induced state with a second

drug while the first continues.

2.6 Acute renal failure

Acute renal failure, taught in current usage as acute kidney injury, is an abrupt decline in kidney function over hours to days, with falling urine output and accumulation of urea, creatinine, potassium and acid, staged by the size of that change. Its causes divide by site in the classical scheme that still organises management. Pre renal failure is underperfusion: volume depletion from bleeding, vomiting, diarrhoea and burns, reduced cardiac output in heart failure and shock of every cause, and the pharmacological underperfusion produced when renin angiotensin blockade and non steroidal anti inflammatory drugs together remove the compensations of a kidney already short of flow, the interaction at the heart of Section 2.9. Intrinsic renal failure is injury within the kidney: acute tubular necrosis from prolonged ischaemia or nephrotoxins, acute interstitial nephritis, glomerulonephritis and vascular injury. Post renal failure is obstruction, prostatic enlargement, stone, malignancy and blocked catheter, the cause that must never be missed because it is the most simply reversed. Presentation is often silent until blood tests declare it, or declares itself by oliguria, breathlessness from fluid overload and acidosis, nausea and encephalopathy in advanced uraemia, and the dangerous electrolyte face of hyperkalaemia with its cardiac effects. Diagnosis reads the trend of creatinine and urine output, separates the three sites by history, examination, bladder assessment and ultrasound excluding obstruction, urine and blood tests seeking intrinsic causes, and review of every medicine and recent contrast study against the timeline.

Pharmacotherapy is chiefly supportive and subtractive, and its principles are examinable precisely because there is no drug that restores injured tubules. Treat the cause: restore perfusion with fluids where depletion is the mechanism and stop where overload forbids them, relieve obstruction, treat sepsis of Unit 3 and glomerular disease specifically. Stop or adjust the nephrotoxic and renally cleared medicines, renin angiotensin agents and metformin among those withheld in the acute illness by standard sick day practice, and review every dose against the reduced clearance. Manage the complications in order of danger: hyperkalaemia by its emergency sequence of cardiac protection, intracellular shift and potassium removal; fluid overload by restriction and loop diuretics where residual function answers; acidosis and uraemic complications by medical therapy and, where refractory, by the dialysis of Section 2.8. Diuretics do not convert or cure intrinsic injury and are not given for that purpose. Recovery is monitored by the returning urine output and falling creatinine, medicines are reintroduced in step with it, and an episode of acute injury is recorded permanently as a risk marker for the chronic disease of the next section.

2.7 Chronic renal failure

Chronic renal failure, chronic kidney disease in current usage, is kidney damage or reduced filtration sustained over months, staged by filtration level and by albuminuria, and progressive in most of its causes toward kidney failure requiring replacement therapy. Its causes are the chronic diseases of the syllabus so far: diabetes first, hypertension and glomerulonephritis next, with polycystic kidney disease, chronic obstruction and reflux, analgesic and other drug injury of Section 2.9, and the cardiovascular diseases with which it shares both causes and consequences. The pathophysiology is loss of functioning nephrons with compensatory hyperfiltration in those remaining, which sustains total function while accelerating their own sclerosis, a self perpetuating cycle that proteinuria marks and worsens; and as function falls, every excretory and endocrine duty of the kidney fails in sequence: sodium and water retention with hypertension and oedema, potassium and acid retention, phosphate retention with secondary hyperparathyroidism and renal bone disease, erythropoietin deficiency with the anaemia of chronic disease, vitamin D activation failure, and accumulation of uraemic toxins affecting heart, brain, blood and immunity. Presentation is silent for most of the course, found on testing in diabetes and hypertension care, and late disease brings fatigue, breathlessness, itch, nausea, restless legs and encephalopathy; cardiovascular death, not uraemia, is the

commonest end of the condition, which is why its management is cardiovascular management too. Diagnosis establishes chronicity, cause, stage and rate of progression, and the complications screen of blood count, calcium, phosphate, parathyroid hormone, potassium and bicarbonate that monitoring then repeats.

Pharmacotherapy pursues three aims: slow progression, treat complications, and prepare for replacement. Progression is slowed by blood pressure control with renin angiotensin blockade as the preferred backbone where proteinuria is present, its kidney protective effect beyond pressure lowering mirroring Part I, by glycaemic control in diabetes, by the SGLT2 inhibitor class whose kidney protection now stands alongside its diabetes and heart failure roles, by salt restriction, smoking cessation and lipid therapy, and by removal of nephrotoxic exposures. Anaemia is treated by correcting iron deficiency and then erythropoiesis stimulating agents under specialist programmes with blood pressure and thrombosis cautions. Mineral and bone disorder is treated by dietary phosphate restriction, phosphate binders taken with food, vitamin D sterols and calcimimetics matched to the parathyroid pattern. Acidosis is corrected with oral bicarbonate in defined practice, potassium managed by diet, binders and review of renin angiotensin and potassium sparing therapy, and every prescription dose reviewed against filtration, the daily arithmetic of renal pharmacy. Vaccination, cardiovascular protection and timely referral for dialysis and transplant planning, with vessels preserved for future access by avoiding needless venepuncture in the chosen arm, complete the plan.

Feature	Acute renal failure	Chronic renal failure
Onset	Hours to days	Months, sustained
Dominant causes	Underperfusion, tubular injury, obstruction	Diabetes, hypertension, glomerular disease, drug injury
Drug task	Stop nephrotoxins, adjust doses, treat complications	Slow progression, treat anaemia and bone disorder, review every dose
Replacement	Only for refractory complications	Planned dialysis or transplantation in kidney failure

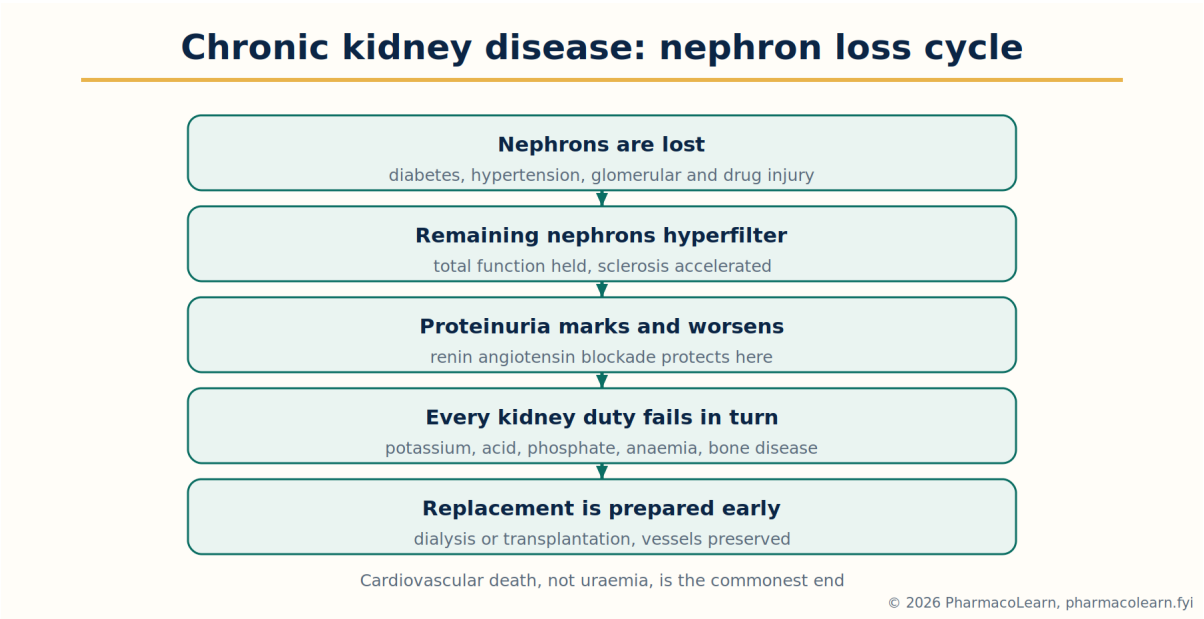

Figure: The nephron loss cycle. Hyperfiltration holds function while accelerating the loss it compensates for.

2.8 Renal dialysis

Renal dialysis is the artificial replacement of the kidney filtration functions that Section 2.7 loses: removal of accumulated small solutes, potassium, acid and water across a semipermeable membrane by diffusion and ultrafiltration, offered when kidney failure produces refractory fluid overload, hyperkalaemia, acidosis, uraemic symptoms or pericarditis, and as planned maintenance therapy in established kidney failure alongside transplantation, which remains the replacement of choice for eligible patients. Haemodialysis passes blood through an extracorporeal dialyser against dialysis fluid, in sessions in a centre or at home, requiring durable vascular access, an arteriovenous fistula created surgically as the preferred access, a graft, or a central venous catheter carrying the highest infection risk; anticoagulation of the circuit, management of intradialytic hypotension from fluid removal, and the disequilibrium of rapid early solute shifts are its therapy problems. Peritoneal dialysis uses the peritoneum as the membrane, dialysis fluid dwelling in the abdomen and exchanged by the patient at home in continuous ambulatory or automated overnight patterns, preserving residual function and independence at the cost of peritonitis risk, glucose absorption from the fluid and eventual membrane failure. Pharmacotherapy around dialysis is a specialty of its own: medicines are removed by dialysis according to their size, protein binding, volume of distribution and water solubility, so dialysis drug dosing asks of every prescription whether the membrane clears it and whether a post dialysis supplement or intradialytic timing is required; the phosphate binders, erythropoiesis agents and vitamin D therapy of Section 2.7 continue as core therapy; heparin exposure brings its thrombocytopenia risk of Part I into view; and transplant pharmacotherapy, immunosuppression balanced against infection and malignancy, waits at the end of the pathway for those who receive a kidney. The pharmacist role is reconciliation across a population taking many medicines with no renal reserve: every new prescription in a dialysis patient is a dosing decision.

2.9 Drug induced renal disease

The kidney concentrates, secretes and is perfused by the drugs it clears, and drug induced renal disease is correspondingly rich in mechanisms, classified for examination by the site and pattern of injury. Haemodynamic injury is the pre renal pattern of Section 2.6 produced pharmacologically: non steroidal anti inflammatory drugs removing prostaglandin mediated afferent dilation, renin angiotensin agents removing efferent tone, calcineurin inhibitors constricting the afferent vessel, and the triple combination of a diuretic with both of the first two classes as the classic prescribing trap in older patients. Acute tubular injury follows direct tubular toxins: aminoglycoside antibiotics accumulating in proximal tubular cells, amphotericin, cisplatin, and contrast media in susceptible patients, with injury declared days into exposure and prevention built on hydration, exposure minimisation and level and function monitoring. Acute interstitial nephritis is the allergic pattern: fever, rash, eosinophilia and sterile pyuria appearing days to weeks into therapy, proton pump inhibitors and beta lactam antibiotics and non steroidal agents prominent among modern culprits, treated by withdrawal and corticosteroids in defined cases, and missed diagnoses scar into chronic disease. Glomerular and vascular patterns include membranous disease, podocyte injury, thrombotic microangiopathy and cholesterol embolisation after vascular instrumentation and anticoagulation. Obstructive patterns arise inside the tubule from crystals, aciclovir, sulfonamides, methotrexate and stone forming metabolic effects, prevented by hydration and urinary alkalinisation where the chemistry allows, and chronic patterns close the list: analgesic nephropathy of historical combination analgesic abuse, lithium associated chronic injury with its diabetes insipidus, and calcineurin inhibitor chronic fibrosis in transplant patients. Management is the constant sequence of this subject: timeline, withdrawal, support, monitoring of recovery, documentation that survives the admission, and counselling where the culprit is an over the counter analgesic the patient never thought to mention.

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