Psychopharmacology in Transplant Patients

42

Martha C. Gamboa and Stephen J. Ferrando

Introduction

The journey of a patient suffering from end-stage organ failure is usually full of pathophysiological alterations and psychosocial challenges. The perspective of organ transplantation brings about its own host of trials. Rates of anxiety and depressive disorders in this population are equal or higher than those in patients with other chronic medical conditions [1, 2]. If not identified and treated appropriately pre- or post-transplant, anxiety and depressive disorders may negatively impact graft and patients' morbidity and mortality outcomes [3]. Neurocognitive disorders are common pre- and post-transplant [4–7]. These disorders can be exacerbated by exogenous substances as well as by other comorbidities and need to be recognized and appropriately treated in order to increase adherence to treatment, optimize quality of life, and improve graft and patient survival [3].

As with any other medically ill patient requiring psychopharmacological interventions, medication choices derive from a careful and comprehensive psychiatric and medical history, a complete mental status examination, collection of collateral information whenever possible, review of pertinent tests, and arrival to a psychiatric diagnosis and differential. In transplant patients, given the severity of their organ failure as well as the possibility of multiple comorbidities, the pharmacological management of psychiatric disorders requires special considerations, including pharmacokinetic, pharmacodynamic, drug-drug interactions and attention to specific medical issues.

M. C. Gamboa (✉) · S. J. Ferrando
Department of Psychiatry and Behavioral Sciences, New York Medical College, Valhalla, NY, USA
e-mail: Martha.gamboa@wmchealth.org

Basic Pharmacological Concepts

Pharmacokinetics

Pharmacokinetics describes the processes and transformations medications undergo in the human body, including absorption, distribution, metabolism and elimination of the drugs and their metabolites.

Absorption

Drug *absorption* refers to the rate at which a pharmacological compound leaves the site of administration and reaches the systemic circulation. *Bioavailability* refers to the percentage of the drug that successfully arrived to the systemic circulation compared to the initial given dose. It depends not only on the drug preparation but on the multiple factors that interfere with absorption in each individual situation. Absorption of a drug requires its pass through cell membranes. Lipid soluble and non-ionized drugs are more easily absorbed than hydrophilic and ionized compounds. The oral route is the most common, inexpensive, and convenient means of drug administration. Most drug absorption from the gastrointestinal (GI) tract occurs by passive diffusion. An orally administered drug reaches the portal vein circulation after crossing the gastric or duodenal enterocyte and the endothelium of the capillary portal vein. The portal vein will carry the drug to the liver. However, the drug may undergo biotransformation at the intestine and the liver prior to reaching the systemic circulation. This process known as the *first pass* decreases drug bioavailability. Other routes of administration, such as the intravenous and sublingual, obviate the process of absorption, hence avoiding hepatic and intestinal first-pass elimination. Drugs that undergo extensive first-pass metabolism require a higher dose when given orally compared to intravenous administration. Factors that alter drug absorption include the surface area for absorption, the physical state of the drug (solid, solution, suspension), its water solubility, the drug concentration at the absorption site,

Y. Sher, J. R. Maldonado (eds.), *Psychosocial Care of End-Stage Organ Disease and Transplant Patients*,
https://doi.org/10.1007/978-3-319-94914-7_42

the presence of food, the presence of other drugs, gastric pH changes, vitamin D deficiency, changes in gastric emptying and intestinal motility, vomiting, intestinal flora, splanchnic blood flow, and the presence of intestinal edema. Additionally, the activity of enterocyte and hepatocyte membrane-embedded transporters such as the ATP-binding cassette (ABC) transporters can block the entrance of substrate drugs into the intestinal wall or into the hepatocyte, thus decreasing drug absorption.

Drug Distribution

Once a drug reaches the systemic circulation, it is distributed throughout the body and its compartments. Factors that alter drug concentration and distribution to tissues and fluids include blood flow, nutritional state, membrane permeability, as well as drug characteristics such as lipophilicity or hydrophilicity, drug pH, and protein-binding capacity. The term *volume of distribution* refers to the relationship between the total amount of drug in the body and the concentration of drug measured in a biological fluid. The volume of distribution seems larger for lipophilic drugs (most psychotropics) as these drugs are sequestered into lipid compartments, rendering low serum levels. The opposite takes place for hydrophilic drugs as they have high serum concentrations, hence, lower volumes of distribution. However, if edema is present, this causes expansion of the extracellular volume and may increase the volume of distribution of hydrophilic drugs, leading to lower serum concentrations.

Drug Metabolism

Drug metabolism refers to the biotransformation of drug compounds into more polar, water-soluble, and inactive molecules that could then be eliminated via urine, bile, or stool. This biotransformation is accomplished by the metabolic enzyme systems largely found in the liver and the intestinal wall, particularly in the smooth endoplasmic reticulum of enterocytes and hepatocytes but also in the intestinal lumen and intestinal microbiota. Metabolic reactions are organized in phases 1 and 2. *Phase 1* reactions are catabolic and involve oxidation, reduction, and hydrolysis processes. The cytochrome P450 (CYP450) mono-oxidase system contributes to the large majority of phase 1 reactions. Some benzodiazepines, such as lorazepam, oxazepam, and temazepam, do not undergo phase 1 metabolic reactions. *Phase 2* reactions are anabolic and involve conjugation reactions, in which water-soluble molecules are added to a drug or metabolite, leading to inactive and polar products easily excreted in the urine. They include glucuronidation, sulfation, and methylation [8]. The activity of phase 1 and 2 enzymes can be induced or inhibited by co-administration of other substances, including drugs, foods, and smoking. Enzyme induction or inhibition can result in lower or higher than desired drug or metabolite levels, potentially causing serious clinical consequences. Additionally, intestinal microorganisms, which include anaerobic bacteria and yeasts, coexist in the human intestine and participate in non-oxidative drug biotransformation reactions such as reduction, hydrolysis, decarboxylation, dehydroxylation, dealkylation, dehalogenation, and deamination. Medications that alter the equilibrium of the gut microbiota can in turn alter the metabolism of co-administered drugs substrates of microorganism enzymes [9, 10]. Other factors that affect drug metabolism include the presence of portosystemic shunts, the quality of the splanchnic blood flow, as well as individual enzyme variations. Recent attention has been given to alterations in the function of CYP450 enzymes by the presence of chronic kidney disease via direct uremic toxins or via inhibition of their expression [11–13].

Elimination

Most drugs and their metabolites are eliminated as polar hydrophilic compounds in the urine. A smaller portion of drugs are eliminated via the hepatobiliary system in the feces. Membrane-embedded transporter systems have an important role in drug elimination. These transporters are present in the intestinal cells, in the hepatocytes, in the renal tubule cells, in the capillary endothelial cells of the blood-brain barrier, as well as in other tissues. Membrane transporters are divided in two superfamilies: solute-linked carrier (SLC) transporters and ATP-linked cassette (ABC) transporters. P-glycoprotein (P-gp) belongs to the later family and is also known as ABCB1 for ATP-binding cassette B1 [14]. When substrate drugs arrive to the intestinal lumen, ABC efflux transporters located in the apical brush border can expel them back to the intestinal lumen. In the enterocyte, substrate drugs undergo phase 1 and 2 metabolism and are subsequently transferred to the portal capillary system. Portal blood carries drugs or their metabolites to the liver. At the hepatocyte level, drugs and their metabolites are transferred by influx (mostly SLC) transporters from the basolateral border to the cytoplasm where the drug undergoes phase 1 and 2 metabolic reactions. The drug metabolites are then transferred mostly via ABC transporters to the bile through the apical border of the cell and then delivered to the duodenum. In the small intestine, drugs can be reactivated by microbiota enzymes and then reabsorbed (enterohepatic circulation) or eliminated in the feces. For example, lorazepam is conjugated in the liver to its inactive metabolite, lorazepam glucuronide. This compound may be excreted in the bile to the intestine, where β-glucuronidase breaks the ester linkage and converts it back to lorazepam, which in turn can be reabsorbed to the portal circulation or eliminated in feces.

The elimination of drugs or their metabolites through the kidney takes place through glomerular filtration, active tubular secretion, and passive tubular reabsorption. Factors limiting glomerular filtration of drugs include molecular size and albumin binding. Only unbound drugs pass freely from

plasma in the glomerular capillary to the glomerular filtrate. Membrane transporters located in the proximal tubule including SLC transporters and ABC transporters including P-glycoprotein secrete drugs into the filtrate. In the proximal and distal renal tubules the non-ionized fraction of the weak acids or bases is passively reabsorbed. The ionized fraction of the drug remains in the filtrate and is excreted in the urine. Additionally, some drugs undergo active reabsorption to the main circulation via membrane transporters located in the distal tubular lumen.

Pharmacodynamics

Pharmacodynamic processes refer to the drug effects on the organism, including the intended and therapeutic, as well as the side effects. Drug effects derive from the interaction between the drug and its receptors and can be altered by the presence of other drugs and medical conditions. Psychiatric medications usually act on multiple receptors; hence potentiation of the effects of other nonpsychiatric drugs is common. For example, amitriptyline is a tricyclic antidepressant which increases the synaptic concentration of serotonin and norepinephrine in the central nervous system by inhibition of their reuptake at the presynaptic neuronal level. However, amitriptyline also has anticholinergic effects, and its concurrent use with diphenhydramine, a histamine H1 antagonist, can increase the risk for side effects, including drowsiness, xerostomia, blurry vision, constipation, and delirium.

Post-transplant Psychopharmacological Issues

The administration of psychiatric medications following organ transplantation should derive from careful review of the patient's overall medical status, the graft function, the level of functioning of the absorbing, metabolizing and eliminating organs, as well as the potential drug-drug interactions, particularly with immunosuppressant agents. Unfortunately, some post-transplant patients suffer primary graft failure requiring early re-transplantation, while others may suffer delayed graft functioning, requiring close monitoring and medication dose adjustments. Once the transplanted organ assumes normal physiological functioning, and proper absorption, metabolism, and elimination are established, medications could be prescribed at their regular doses. Acute rejection occurs in approximately 20% of liver transplant patients in the first 6 months after surgery [15], in 10% of intestinal transplant recipients within the first month [16, 17], in up to 60% of kidney transplant patients in the first 6 months, and in up to 50% of heart transplant patients within the first year [16]. Acute graft rejection usually requires more aggressive management with immunosuppressant agents [18], including high-dose steroids, which themselves can cause a wide variety of neuropsychiatric symptoms.

Initial postoperative psychopharmacological interventions usually focus on management of delirium and neuropsychiatric side effects from immunosuppressants, as well as treatment of anxiety related to perceived traumatic perioperative events such as intense uncontrolled pain, intubation, inability to communicate, and the use of restraints. Following the acute recovery phase, additional indications for psychopharmacological interventions include the presence of anxiety and/or depressive symptoms interfering with recovery, adjustment to medications side effects, decreased appetite, and insomnia. Long-term, post-transplant patients have to deal with the fear of rejection, body image issues, acceptance of role changes, financial concerns, hospital bills, cravings for smoking, alcohol or other substances, as well as re-hospitalizations in the context of organ rejection or immunosuppression-related complications. These include neurocognitive impairments, serious infections, increased cancer risk, and compromise of kidney function in some cases leading to initiation of renal replacement therapy. Mental health professionals caring for transplant patients need to be alert to patients' post-transplant biopsychosocial changes and adaptations. Additionally, it is important to understand basic aspects of immunosuppressants commonly used in post-transplant patients in order to confidently recognize their psychoactive side effects, as well as recommend and prescribe psychiatric medications when needed.

Immunosuppressants

Important nonspecific immunosuppressant side effects include weight gain, hypertension, diabetes, and dyslipidemias [19, 20]. These comorbidities are important to consider when deciding on the addition of a psychopharmacological agent, given that many psychotropics are associated with weight gain and metabolic syndrome.

Corticosteroids

Steroids play an important role in transplantation at various stages, including induction, maintenance, and management of rejection. Steroids bind to glucocorticoid-responsive elements in DNA preventing the transcription of cytokine genes and receptors. They also decrease cell-mediated immunity and T-cell activation. Methylprednisolone, prednisolone, and prednisone are substrates of CYP3A4. At high doses glucocorticoids inhibit and at low doses induce CYP3A4. Several psychiatric drugs are either inducers or inhibitors of CYP3A4; therefore, drug-drug interactions are expected when used concurrently [20]. Common neuropsychiatric side effects of glucocorticoids include agitation, anxiety,

cognitive impairments, delusions, delirium, euphoria, hallucinations, as well as personality changes [21]. The most validated risk factor for these side effects is the dose, particularly doses higher than 40 mg per day [21]. Other risk factors include blood-brain barrier damage, hypoalbuminemia and co-administration of CYP 3A4 inhibitors [21]. On the other hand, depressed mood, fatigue, mania, and delirium can occur upon withdrawal of steroids [21–23].

It is important to educate patients and caregivers regarding the possibility of steroid-induced neuropsychiatric adverse effects including changes in mood and cognitive abilities. A history of mood disorders as well as previous neuropsychiatric adverse reactions to steroids alerts the clinician about the need to consider prophylactic interventions. Unfortunately, there is a paucity of well-powered randomized controlled trials informing on the efficacy and safety of specific agents for this purpose. Similarly, the literature on the treatment of steroid-induced neuropsychiatric disorders is based on multiple case reports and small trials. For steroid-induced mania in the transplant population, the reduction and discontinuation of the steroid dose are not always possible, and the temporary addition of a neuroleptic such as olanzapine could be considered a first step [21, 24, 25]. In this case, the monitoring of glucose control should be emphasized. The use of lithium is second choice due to nephrotoxicity concerns in the presence of calcineurin inhibitors and potential co-administration of diuretics. Antiepileptics can also be used, including valproic acid and gabapentin [24, 26]. Benzodiazepines can also be helpful, particularly clonazepam [27].

Calcineurin Inhibitors (CNIs)

Tacrolimus and cyclosporine are the cornerstone drugs in solid organ transplantation [19]. Although they are not chemically related to each other, they have similar mechanisms of action since they both bind to cytoplasmic isomerases that are abundant in all tissues. Cyclosporine binds to cyclophilin and tacrolimus binds to the immunophilin FK-binding protein (FKBP) forming complexes that inhibit calcineurin. Calcineurin is a cytoplasmic phosphatase necessary for the activation of a T-cell-specific transcription factor involved in the synthesis of interleukins by activated T cells. CNIs are highly lipophilic and undergo extensive first-pass metabolism. They are substrates for the cytochrome CYP3A4, CYP3A5, as well as the P-glycoprotein transporter.

Since these medications have pharmacokinetic and pharmacodynamic variability, therapeutic drug monitoring is routine. Low blood levels increase risk of rejection, while high levels increase risk of adverse effects, including neurotoxicity, nephrotoxicity, infection, and neoplasias. Due to individual variability, rejection as well as toxicities can occur within therapeutic drug levels. The mechanism underlying CNIs' neurotoxic effects is not yet well understood, but it may be related to the role of calcineurin in neuronal cell functioning [28]. Tacrolimus and cyclosporine may cause similar neuropsychiatric side effects, including agitation, anxiety, cognitive impairment, depression, dysarthria, fatigue, hallucinations, insomnia, lethargy, neuropathy, and seizures [19, 29]. Both agents have also been associated with the development of posterior reversible encephalopathy syndrome (PRES), a rare neurologic condition presenting in approximately 0.5–5% of solid organ transplant patients [30–32]. The characteristic clinical symptoms in post-transplant PRES include seizures, headache, acute encephalopathy syndrome, autonomic instability, and visual symptoms, while magnetic resonance imaging (MRI) findings consist of an abnormal and reversible increased signal in the fluid-attenuated inversion recovery (FLAIR) images, with characteristic distribution in the parietal and occipital lobes, and less frequently in the posterior frontal, temporal lobe, cerebellum, brainstem, thalamus, and basal ganglia [33, 34]. Early diagnosis is important, although there is no clear consensus regarding immunosuppressant management in this context. Some studies recommend a decrease and even a complete discontinuation of CNI and switching to other immunosuppressant agents [35].

Long-term neuropsychiatric side effects of CNIs include cognitive impairment and tremors [19].

In addition, the long-term use of CNIs can lead to nephrotoxicity [19]. This emphasizes the need to monitor renal function particularly when medications that do not undergo liver metabolism and that are fully or almost fully eliminated by the kidney are co-administered (i.e., gabapentin, amantadine, lithium).

Cyclosporine

This agent is available for oral and intravenous administration. The oral absorption of cyclosporine is erratic and incomplete and depends on the presence of food, bile acids, and gastrointestinal motility [36]. Cyclosporine is extensively metabolized in the liver via CYP3A4, forming many metabolites, and it undergoes extensive first-pass effect following oral administration. In plasma, cyclosporine is both a substrate and an inhibitor of CYP3A4 and P-glycoprotein. Given that many psychiatric drugs are metabolized by CYP3A4, there are multiple possibilities for significant drug-drug interactions [29]. Psychiatric drugs that inhibit CYP3A4, such as fluvoxamine, nefazodone, and fluoxetine, can increase cyclosporine levels and risk of toxicity. On the other hand, CYP3A4 inducers, such as carbamazepine, phenobarbital, and modafinil, can decrease cyclosporine levels risking transplant rejection. Furthermore, since cyclosporine itself is an inhibitor of CYP3A4, it can increase the levels of buspirone, most benzodiazepines, iloperidone, quetiapine, and ziprasidone. Additionally, P-glycoprotein inducers, such as *Hypericum perforatum* (i.e., St. John's wort), can also induce

CYP3A4 [37] and thus reduce cyclosporine levels, increasing risk of rejection. Since cyclosporine inhibits P-glycoprotein, it can increase the bioavailability of several psychiatric medications including carbamazepine, lamotrigine, olanzapine, phenytoin, paroxetine, quetiapine, risperidone, and venlafaxine, among others. Cyclosporine can cause hyperkalemia by decreasing potassium tubular excretion. This may be a mechanism underlying its association with increased cardiac arrhythmia risk [38]. Therefore, concurrent use of cyclosporine and potentially arrhythmogenic psychiatric drugs needs to be executed under careful monitoring.

Tacrolimus

Tacrolimus is available for intravenous and oral administration. Its oral absorption is incomplete and variable and also reduced in the presence of food. Tacrolimus is highly protein bound to plasma proteins: 99% is primarily bound to albumin and alpha1 acid glycoprotein. This CNI is metabolized extensively in the liver via CYP3A4 to several metabolites. Tacrolimus is a substrate of P-glycoprotein. It is also a substrate and inhibitor of uridine 5′-diphosphate glucuronosyltransferase (UGT). Tacrolimus use can be associated with QT prolongation [39, 40]. Given that many psychotropic agents can prolong the QT interval [41] and that they often are substrates and/or inhibitors of CYP3A4, caution is advised when they are co-administered with tacrolimus. Close monitoring of the electrocardiogram, tacrolimus levels, as well as serum electrolytes including sodium, potassium, and calcium is advised. Drug dosage reduction may be necessary.

Mechanistic Target of Rapamycin (mTOR) Inhibitors

Sirolimus and everolimus exert their principal immunosuppressive effects by inhibiting the ability of the cytoplasmic enzyme complex mTOR to regulate the growth, proliferation, and survival of lymphocytes and other immunocompetent cells. Sirolimus and everolimus are metabolized in the liver and intestinal wall by CYP3A4 and CYP3A5 and, to a minor extent, by CYP2C8. They are both substrates of ABCB1, while everolimus has inhibitory action on CYP3A4 and ABCB. Its metabolites are excreted primarily in feces. Neuropsychiatric side effects include tremor, insomnia, headache, and pain [42].

Polyclonal and Monoclonal Antibodies

Antithymocyte globulin (ATG) is a purified gamma globulin obtained by immunizing rabbits (thymoglobulin) or horses (Atgam) with human thymocytes [43, 44]. ATG induces lymphocyte depletion in the periphery by complement-dependent cell lysis. Premedication with steroids, acetaminophen, and/or antihistamine approximately 1 h prior to infusion is recommended to minimize the antithymocyte globulin-induced cytokine release syndrome, characterized by fever, chills, and rigors, but can also include dyspnea, nausea/vomiting, diarrhea, hypotension, hypertension, malaise, rash, and headache The metabolism and elimination of this drug is unknown. The principal neuropsychiatric side effects of thymoglobulin include chills, pain, headache, malaise, and anxiety [43, 44].

Basiliximab is a monoclonal antibody that blocks the T-cell IL-2 receptor preventing IL-2-induced T-cell activation [45]. Basiliximab is a powerful induction agent, but it is not used to treat acute rejection, as it does not cause lymphocyte depletion. Common neuropsychiatric adverse effects include insomnia, fatigue, pain, headache, tremor, agitation, anxiety, and depression [45].

Alemtuzumab is a monoclonal antibody that has profound lymphocyte-depleting effects [46, 47]. It causes cell death by complement-mediated cytolysis, antibody-mediated cytotoxicity, and apoptosis. Alemtuzumab causes a long-lasting T-cell depletion, which prolongs infection and lymphoproliferative disorder risks. Psychiatric adverse effects include insomnia, anxiety, and suicidal ideation [46, 47].

Rituximab is a monoclonal antibody that binds specifically to a B-lymphocyte differentiation antigen on pre-B- and mature B-lymphocytes [48]. Neuropsychiatric side effects include anxiety, chills, delirium, depression, dizziness, fatigue, insomnia, migraine, myalgias, neuropathy, paresthesias, and pain [48].

Inhibitors of Purine Synthesis

Mycophenolate Mofetil

The active drug mycophenolic acid inhibits inosine-5′-monophosphate dehydrogenase (IMPDH), a rate-limiting enzyme in the purine synthesis. Mycophenolic acid suppresses the proliferation of T- and B-lymphocytes. Common neuropsychiatric side effects include pain, headache, dizziness, tremor, insomnia, and anxiety [49].

Azathioprine

Azathioprine is metabolized to 6-mercaptopurine (6-MP). 6-MP substitutes the purine base guanine in RNA. Mercaptopurine ribonucleotides are incorporated into RNA and halt DNA synthesis. The immunosuppressive activity of azathioprine is due to its ability to inhibit delayed hypersensitivity reactions and cellular cytotoxic activity. Neuropsychiatric side effects include malaise and myalgias [50].

Others

Belatacept is a selective T-cell costimulation blocker. This medication is indicated for rejection prophylaxis in adults receiving kidney transplant. Neuropsychiatric side effects include anxiety, dizziness, headache, insomnia, pain, tremor, and Guillain-Barre syndrome, and it has been implicated in post-transplant lymphoproliferative disorder (PTLD) [51].

Psychiatric Medications

Antidepressants

Antidepressants are commonly used in the transplant population to assist in the management of various psychiatric syndromes, including depression, anxiety, insomnia, pain, and appetite stimulation.

Selective Serotonin Reuptake Inhibitors (SSRIs)

Among transplant patients, most SSRI studies have taken place in patients with end-stage heart or kidney disease [13, 52–54]. As a family, SSRIs share some side effects.

SSRIs increase bleeding risk as they inhibit platelet activation and thus may increase bleeding time [55, 56]. This can be particularly problematic in end-stage liver disease, since patients with cirrhosis are prone to bleeding in the context of coagulopathy, thrombocytopenia, and variceal formation. Additionally, platelet dysfunction can also be present in patients with kidney failure. Many end-stage organ disease patients are managed with anticoagulants and/or aspirin, and special caution needs to be taken when co-administration of an antidepressant is needed.

All SSRIs can potentially prolong QT interval; therefore, caution is needed in the context of predisposing medical conditions and co-administration with other QT prolonging drugs [41]. Of note, of the SSRI agents, citalopram is associated with the most QT prolongation [41]. In addition, SSRIs have been associated with hyponatremia [57, 58]. The use of SSRI agents has been associated with bone metabolism dysfunction; thus they may increase the risk for fractures. Therefore, caution is required when use in the context of chronic corticosteroid therapy [59]. Despite of these potential issues, SSRIs remain the first-line treatment for the treatment of depression in transplant patients due to their superior safety profile and less drug-drug interactions when compared to other antidepressants [60].

Sertraline

Sertraline is well absorbed after oral administration. It is 98% protein bound and is metabolized by CYP3A4 to desmethylsertraline [61]. At low doses the parent drug and its metabolite cause weak inhibition of CYP2D6, which can become clinically relevant at high doses [62, 63]. Sertraline does not inhibit CYP3A4 in vivo [64], which is favorable for patients taking immunosuppressant agents. However, at least one study found an association of sertraline and increased cyclosporine levels [65]. Sertraline elimination half-life increases in the context of liver failure. Sertraline has been helpful in decreasing pruritus in cholestatic jaundice patients, which constitutes an added benefit in this clinical scenario [66]. It has been shown to be helpful for sensation of dyspnea in patients with chronic obstructive pulmonary disease [67]. In addition, sertraline has been helpful in reducing dialysis-related hypotension which makes this medication appealing in patients with difficulty tolerating dialysis [68]. Dose adjustment is not recommended in kidney failure. However in mild liver failure, it is advised to decrease the dose to half of the usual. Furthermore, in moderate to advanced liver failure, sertraline is not recommended [69].

Citalopram

Citalopram is composed of S and R enantiomers. The S enantiomer (escitalopram) is pharmacologically active. Citalopram is absorbed rapidly following oral administration and is metabolized by CYP3A4 and CYP2C19 [61]. Citalopram is a weak inhibitor of 2D6, and concurrent administration with metoprolol leads to increased levels of the beta-blocker [70]. Citalopram has the Food and Drug Administration (FDA) warning regarding its potential to prolong QT [41]. Citalopram is also the only agent that carries specific recommendations, including a maximum daily dose of 20 mg/day in patients suffering with hepatic impairment or in those older than 60 years and a maximum 40 mg dose/day in young and healthier patients [71], although the merit of this warning has been debated [72].

Escitalopram

The S enantiomer of citalopram is rapidly absorbed following oral administration. Escitalopram is 56% protein bound [61]. It is metabolized by CYP2D6, 2C19, and 3A4 and weakly inhibits CYP2D6 [61]. Dose adjustment is recommended in hepatic and severe renal impairment [69]. QT can still be prolonged by escitalopram, although to a lesser degree compared to citalopram [41].

Paroxetine

Paroxetine is metabolized by CYP2D6, strongly inhibits CYP2D6, and has a mild inhibitory effect of CYP2C9 and CYP2C19 [61]. Paroxetine has significant anticholinergic properties, which can contribute to many side effects, including delirium and cognitive impairment. It has a relatively short half-life, which may be associated with severe serotonin withdrawal, upon abrupt discontinuation. In addition, its use is associated with significant weight gain, as compared to other SSRIs. In severe renal (creatinine clearance <30%) and hepatic impairment, the manufacturer recommends slower titration and lower maximum daily dosages.

Fluoxetine

Fluoxetine is metabolized by CYP2D6 and CYP2C9 [61]. Fluoxetine and its active metabolite, norfluoxetine, inhibit CYP2D6, CYP2C9, CYP2C19, and CYP3A4 [61]. Fluoxetine has the longest half-life of all the SSRIs (i.e., 7 days) [69]. In patients with severe impaired renal function, additional accumulation of fluoxetine and norfluoxetine may occur. Patients with liver cirrhosis require lower than usual doses or less frequent administration intervals.

Fluvoxamine

Fluvoxamine is metabolized primarily by deamination and acetylation. Fluvoxamine is a substrate of CYP1A2 and CYP2D6 [61]. This drug is a potent inhibitor of CYP1A2 and exerts less inhibition of CYP2C19, CYP2C9, and CYP3A4. There is limited information regarding its safety in kidney and liver impairment. Due to its significant potential for interactions, it is usually avoided in the transplant population.

Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)

SNRIs are chemically unrelated to each other. As in the case of tricyclic antidepressants (TCAs), SNRIs inhibit serotonin and norepinephrine reuptake [61]. However, in contrast to TCAs, SNRIs do not have much affinity for other receptors. In addition to their use in major depression, SNRIs may be useful in the treatment of pain disorders. SNRIs are associated with increases in blood pressure and heart rate; therefore, caution is recommended in patients with hypertension, cerebrovascular disease, and cardiac disease.

Venlafaxine

Venlafaxine is a potent inhibitor of neuronal serotonin and norepinephrine reuptake and weak inhibitor of dopamine reuptake [61]. Venlafaxine functions like an SSRI in low doses and as a dual mechanism agent affecting both serotonin and norepinephrine at doses above 225 mg per day. Venlafaxine has a short half-life and is associated with increased risk of serotonin withdrawal. Venlafaxine is metabolized by CYP2D6. Two cases of serotonin toxicity have been reported in patients receiving venlafaxine and CNIs, likely due to CNI-inhibitory effect of P-glycoprotein [73]. Dose reduction of venlafaxine is indicated in kidney and liver impairment.

Desvenlafaxine

Desvenlafaxine is the major active metabolite of venlafaxine [61]. Desvenlafaxine undergoes hepatic metabolism primarily by conjugation and in less proportion by oxidation via CYP3A4. Desvenlafaxine is a weak inhibitor of CYP2D6 and a weak inductor of CYP3A4; however, clinical studies have not found clinically relevant interactions when this medication is co-administrated with CYP2D6 and CYP3A4 substrates, at doses up to 100 mg/day. Desvenlafaxine dosing needs to be adjusted in the setting of renal and hepatic impairment [74].

Duloxetine

Duloxetine is metabolized by the liver, via CYP1A2 and CYP2D6 into multiple inactive metabolites [61]. Duloxetine is associated with increased risk of idiopathic hepatic failure [75, 76]. Duloxetine use should be avoided in hepatic impairment and in cases of kidney failure with creatinine clearance lower than 30 mL/min.

Milnacipran

Milnacipran is a SNRI that has been used in the treatment of depression in Europe for many years but only approved in the USA for the treatment of fibromyalgia. Milnacipran undergoes hepatic metabolism and should be used with caution in kidney and liver impairment. Its dosage should be reduced if the creatinine clearance is lower than 30 mL/minute and its use is not recommended in end-stage renal disease. However, the manufacturer does not recommend dose adjustment in case of hepatic impairment.

Levomilnacipran

Levomilnacipran is an enantiomer of racemic milnacipran. Levomilnacipran is metabolized in the liver primarily by CYP3A4 to inactive metabolites. Levomilnacipran is a weak substrate of P-glycoprotein. More than half of the dose of levomilnacipran is excreted by the kidney. Dosage adjustment is needed in the context of renal impairment with creatinine clearance lower than 30 mL/min.

Other Antidepressants

Mirtazapine

Mirtazapine has central presynaptic alpha$_2$-adrenergic antagonist effects, leading to increased release of norepinephrine and serotonin [61]. Additionally it is a potent antagonist of 5-HT$_2$ and 5-HT$_3$ serotonin receptors and H$_1$ histamine receptors and a moderate antagonist at peripheral alpha$_1$-adrenergic and muscarinic receptors. Mirtazapine is metabolized by CYP2D6, CYP1A2, CYP3A4, and CYP2C9 [61]. This medication has been associated with rare potentially life-threatening agranulocytosis [77]; therefore, caution is necessary when given concurrently with immunosuppressant agents and in patients before and after hematopoietic cell transplantation. Common side effects include sedation, increased appetite, and weight gain, which are desirable effects in patients who need to increase oral intake and improve sleep, particularly pre-transplant. Mirtazapine does not inhibit CYP enzymes. By blocking 5-HT2A receptors, mirtazapine potentially blocks JC virus from entering into glial cells, and for this reason, it has been used in the treatment of progressive multifocal leukoencephalopathy (PML), a condition that can occur in immunosuppressed patients. However, data on transplant patients treated with mirtazapine for PML is scarce, and the level of evidence supporting mirtazapine use in this scenario is low so far [78]. Mirtazapine clearance is decreased in the context of kidney and liver impairment.

Vilazodone

Vilazodone inhibits the reuptake of serotonin and is a 5-HT1A receptor partial agonist. It is metabolized mainly by CYP3A4; thus caution should be used when combined with immunosuppressant agents. Vilazodone is metabolized in less degree by 2C19 and 2D6 [79]. No dose adjustments are reportedly needed in renal or hepatic impairment based on small studies.

Nefazodone

Nefazodone inhibits neuronal reuptake of serotonin and norepinephrine and also blocks 5-HT and alpha1 receptors [61]. Nefazodone is rapidly absorbed following oral administration. Nefazodone is metabolized by CYP3A4 and CYP2D6, and it is an inhibitor of CYP3A4. It also exerts weak inhibition of CYP2D6 [80]. It undergoes extensive first pass, with a bioavailability of 20%. It is 99% protein bound. Nefazodone has been associated with rare cases of acute liver failure, leading to liver transplantation and death in few, and its product label has a black box warning to this respect [81]. For this and its potential for drug-drug interactions, nefazodone is not recommended in transplant patients.

Trazodone

Trazodone inhibits the reuptake of serotonin and acts as a 5-HT2a receptor antagonist [61]. Additionally, trazodone blocks H_1 histamine and alpha1-adrenergic receptors, mechanisms involved in its sedative effect. Trazodone is rapidly absorbed after oral administration. Its concentration peaks at 1 hour. It is 90% protein bound and its bioavailability is 80%. It is metabolized by CYP3A4 and CYP2D6 and it does not seem to inhibit or induce CYP enzymes. It is associated with orthostatic hypotension due to its alpha1-adrenergic effects. Trazodone should be used with caution in patients with kidney and/or liver impairment due to the possibility of accumulation, reduction in its excretion, and increased risk of side effects.

Vortioxetine

Vortioxetine inhibits the reuptake of serotonin and has agonist activity at the 5-HT_{1A} receptor and antagonist activity at the 5-HT_3 receptor. Vortioxetine is metabolized by CYP2D6 isoenzyme. Its use in severe hepatic impairment is not recommended. Dosage adjustment is recommended for CYP2D6 poor metabolizers and when given concurrently with strong CYP2D6 inhibitors.

Bupropion

Bupropion is a relatively weak inhibitor of the neuronal uptake of norepinephrine and dopamine, and does not inhibit monoamine oxidase or the reuptake of serotonin [61]. Bupropion is a substrate of CYP2B6 and a strong inhibitor of CYP2D6 [61]. Dose needs to be adjusted in end-stage liver disease. Bupropion lacks sedative side effects; hence it is an alternative for patients suffering from decreased energy. It is also used for smoking cessation [61]. It can cause tachycardia and increased blood pressure [61]. It can decrease seizure threshold, especially in patients with electrolyte abnormalities or structural brain abnormalities.

Monoamine Oxidase Inhibitors (MAOIs)

By inhibiting the monoamine oxidase enzyme, MAOIs (tranylcypromine, phenelzine, isocarboxazid, selegiline) increase monoamine concentrations in the presynaptic neuron [61]. These monoamines include dopamine, tyramine, serotonin, norepinephrine, epinephrine, and phenylethylamine. There are two monoamine oxidase isoenzymes: A and B. MAO-A is found primarily in the brain, liver, gut, and placenta; its primary substrates are norepinephrine, epinephrine, and serotonin. MAO-B is found in the brain, liver, and platelets; its main substrates are dopamine, phenylethylamine, histamine, and tyramine. Some MAOIs inhibit both isoenzymes (A and B) and are irreversible inhibitors, while others are selective for one or the other and are mostly reversible inhibitors. Most MAOIs produce a nonspecific reduction in the activity of hepatic drug-metabolizing enzymes. MAOIs inhibit MAO in the gut which can lead to life-threatening tyramine pressor effects. Due to drug-drug and food-drug potential interactions, MAOIs are not considered as first line in the treatment of depression in patients with medical comorbidities, including transplant candidates and recipients [69, 82].

Tricyclic Antidepressants (TCAs)

TCAs' tolerability and lethality in overdose have placed them as second choice in the management of depression, behind SSRIs. By virtue of their involvement in the blockade of several receptors, including acetylcholine muscarinic, alpha1, and histamine receptors, the use of TCA increases the risk of arrhythmias, QTc prolongation, intraventricular conduction delays, orthostatic hypotension, weight gain, as well as lipid changes. Use of TCAs in the transplant population requires careful follow-up [69]. TCAs are metabolized by the CYP system. Secondary amines such as desipramine, nortriptyline, and protriptyline are primarily substrates of CYP2D6, while tertiary amines such as imipramine, clomipramine, and amitriptyline are substrates for CYP1A2 and CYP2C19. Dose adjustment is necessary in kidney and liver impairment.

Herbal Supplements

Patients might be using herbal supplements; thus it is important to inquire about this use and properly counsel patients. For example, St. John's wort, an herbal known for its antidepressant actions, extracted from the plant *Hypericum perforatum*, is actually an inducer of 3A4 and P-glycoprotein [83]. In fact, concurrent use of St. John's wort and cyclosporine has caused graft rejections [83–85].

Stimulants

Besides attention deficit and hyperactivity disorders, psychostimulants can be used in the treatment of apathy and depression, when faster effect is needed [86]. In 2006, the FDA requested that all manufacturers of stimulant medications include a class label change that sudden death has been reported in pediatric patients with structural cardiac abnormalities receiving stimulants [87]. Prior to initiation of stimulants, patients need to be evaluated for possible heart conditions including physical examination, electrocardiogram, and family history of cardiac illness.

Methylphenidate

Methylphenidate blocks dopamine uptake in central adrenergic neurons by blocking dopamine transport proteins. This causes increase of the sympathomimetic activity in the central nervous system. Methylphenidate is available for oral and transdermal administration. Methylphenidate is not metabolized by the CYP system, and it does not seem to be an inhibitor of CYP isozymes. Instead, methylphenidate is metabolized via de-esterification to its main metabolite, ritalinic acid, which is inactive and is eliminated by the kidney. This drug has not been studied in renal or hepatic impairment.

A small retrospective study in liver transplant patients targeting psychomotor and cognitive slowing, lack of motivation for recovery, poor rehabilitation effort, social withdrawal, and apathy found positive effect from methylphenidate [88]. A recent meta-analysis also provided further support for efficacy of methylphenidate in treatment of fatigue in patients with cancer and those undergoing hematopoietic cell transplantation [89]. Patients need to be monitored for risk of developing tachyarrhythmias and hypertension. A case report described the successful use of methylphenidate in a patient with heart transplant and depression who developed catatonic symptoms after initiation of sertraline [90]. However, a recent publication also reported a case of a 12-year-old child who developed liver failure, requiring liver transplantation, presumed to be associated with methylphenidate hepatotoxicity [91].

Dextroamphetamine

Dextroamphetamine is the D-isomer of amphetamine and is twice as potent as racemic amphetamine. Escalating doses of dextroamphetamine produce the progressive release of norepinephrine, dopamine, and serotonin from storage sites in the nerve terminal. Dextroamphetamine is available in oral presentation. Its metabolism is hepatic, via CYP monooxygenase and glucuronidation, with renal elimination. Renal and hepatic impairment may lead to decreased elimination and prolonged exposure; therefore, doses should be titrated carefully [92].

Modafinil

Modafinil mechanism of action is not fully understood. It appears that modafinil induces alertness by activating wakefulness-related systems such as hypocretin, histamine, α-adrenergic, glutamate, and dopamine, likely by blocking the activity of the dopamine transporter and modulating norepinephrine and serotonin transporters [93]. Dose reduction is recommended in patients with severe hepatic impairment. Elimination half-life is around 15 hours. Modafinil is metabolized by and weakly induces CYP3A4; thus it can hypothetically lead to decreased blood levels of immunosuppressants also metabolized by CYP3A4. Elimination is mostly hepatic, with kidney excretion of inactive metabolites.

Benzodiazepines

Benzodiazepines produce central nervous system depression including sedation, skeletal muscle relaxation, anticonvulsant activity, and coma by interacting with gamma aminobutyric acid A (GABA-A) receptors. Potentiation of GABA effects increases the inhibition of the ascending reticular activating system. The use of benzodiazepines in patients with end-stage organ disease requires vigilance due to the potential to cause excessive sedation, respiratory depression (worsened by co-administration of opioids), increased risk of falls, and worsened cognition. Some benzodiazepines such as diazepam, lorazepam, and midazolam are available for parenteral use. In liver disease, oxazepam, temazepam, and lorazepam are preferred as they do not undergo phase 1 metabolism (i.e., oxidation), but only phase 2 by glucuronidation. Benzodiazepines act within few minutes of administration, which makes them very appealing for rapid anxiety relief. Due to their potential for tolerance and cognitive decline in the longer term, prolonged use of benzodiazepines should be avoided. Their use pre- and post-transplant can also increase risk of delirium. Cigarette smoking may increase clearance of alprazolam, lorazepam, oxazepam, diazepam, and demethyldiazepam [94].

Lorazepam

Its availability for oral, intravenous, and intramuscular use makes lorazepam a very appealing medication in many settings. Lorazepam elimination half-life is 12–15 hours and protein binding is around 90%. Its metabolite, lorazepam glucuronide, is inactive and excreted in urine. Use in severe renal impairment is not recommended. Use in severe hepatic impairment requires caution and dose adjustment.

Clonazepam

Clonazepam is orally administered. It undergoes extensive hepatic metabolism including involvement of the CYP system as well as conjugation reactions. Its metabolites are

inactive and undergo renal excretion. Clonazepam is 85% bound to proteins. Its half-life eliminations is 17–60 hours in adults. In renal and hepatic impairment, clonazepam should be used with caution due to risk of accumulation.

Alprazolam

Alprazolam is available for oral use. Extended release presentations are available. Alprazolam undergoes metabolism via CYP3A4 to active and inactive metabolites, which do not appear to be clinically significant. Protein binding is around 80–90%. Elimination of immediate release formulations is between 6 and 16 hours. Dose adjustment in advanced hepatic impairment is necessary. Pharmacokinetic studies in special populations such as in patients with liver or kidney impairment are lacking for the extended release formulation.

Other

Buspirone

Buspirone is a non-benzodiazepine anxiolytic used in the treatment of generalized anxiety disorder. Its mechanism of action is not well understood, but it is likely through suppression of serotonergic activity and enhancement of noradrenergic and dopaminergic cell firing [95]. Its main action seems to be a partial agonism of 5-HT1A receptors. Buspirone undergoes extensive first-pass effect, and it is metabolized via hepatic oxidation, primarily via CYP3A4 to active and inactive metabolites. Buspirone elimination half-life is 1–10 hours. Anxiolytic activity starts around 4 weeks into the initiation. Use in patients with pulmonary pathology may be advantageous given its lack of respiratory depression. Half-life elimination is prolonged in renal and hepatic impairment. The administration of buspirone in advanced kidney and liver disease is not recommended.

Antipsychotics

Typical and atypical antipsychotics are used in the transplant population for treatment of preexisting and new onset psychosis and mood disorders, delirium, and refractory anxiety. Antipsychotic use in the post-transplant patients brings about concerns related to QTc prolongation [41], particularly when co-administered with tacrolimus which can also prolong the QT and/or cyclosporine which could increase the risk of arrhythmia.

Typical Antipsychotics

Haloperidol

Haloperidol is a high-potency typical antipsychotic. The therapeutic effect in the treatment of positive psychotic symptoms is thought to result from the central postsynaptic dopamine-2 receptor blockade in the mesolimbic pathway [96]. Haloperidol is available for oral and parenteral (i.e., IM and IV) administration. Intravenous use of haloperidol is not approved by the FDA; however, it is frequently used in the intensive care setting where cardiac monitoring is continuous and for the management of postoperative agitation and/or delirium or immunosuppressant-induced psychotic symptoms. Haloperidol is metabolized by glucuronidation and via CYP2D6 and CYP3A4 isozymes, to inactive metabolites. Haloperidol is 90% protein bound. No dose adjustment is needed in renal or hepatic impairment. Frequent monitoring of QTc for potential prolongation is recommended. Pseudoparkinsonism and other extrapyramidal symptoms can result from dopamine blockade in the nigrostriatal pathway; therefore, this is an additional aspect that requires close monitoring, taking into account that calcineurin inhibitors can cause myoclonus and tremors. Slow CYP2D6 metabolizers may be at increased risk for haloperidol side effects.

Atypical Antipsychotics

Atypical antipsychotics can increase risk of dyslipidemias, obesity, glucose intolerance, and hypertension [96]. In the transplant setting, this side effect profile represents an added concern given the similarities with that of the immunosuppressant agents.

Aripiprazole

Aripiprazole is available in oral and intramuscular extended release forms. The oral forms include tablet, disintegrated tablet, and solution. The mechanism of action of aripiprazole is unique among antipsychotics due to its partial agonism of dopaminergic D-2 receptors. It is also a partial agonist of 5-HT1A receptors and an antagonist of 5-HT2A receptors. This medication seems to be one of the least QTc prolonging among the antipsychotics [41]. Aripiprazole is metabolized by CYP3A4 and CYP2D6 to an active metabolite, dehydroaripiprazole. No dose adjustment is needed in hepatic or renal impairment. The elimination half-life of immediate release aripiprazole is 75 hours and 94 hours for dehydroaripiprazole. For poor CYP2D6 metabolizers, half-life elimination of aripiprazole is 146 hours [97].

Olanzapine

Olanzapine can be administered by mouth in the forms of regular tablet form and orally disintegrated tablet. Olanzapine is also available for intramuscular administration in immediate and extended release injections. Olanzapine is a potent antagonist of serotonin 5-HT2A and 5-HT2C, dopamine D 1–4, histamine H1, and alpha1-adrenergic receptors [96]. Olanzapine has moderate antagonism of 5-HT3 and muscarinic M1–5 receptors. Olanzapine is metabolized by direct glucuronidation and oxidation via CYP1A2 and CYP2D6. Cigarette smoking may alter its metabolism via CYP1A2 induction. Olanzapine dose does not need to be adjusted in

renal impairment and is not dialyzable. Olanzapine dose does not require adjustment in liver impairment except when given in combination with fluoxetine. In that case the manufacturer recommends that the initial olanzapine dose should be limited to 2.5 to 5 mg daily [98].

Quetiapine

Quetiapine is available in immediate and extended release oral forms. Quetiapine is an antagonist of serotonin 5-HT1A and 5-HT2, dopamine D1 and D2, histamine H1, and adrenergic alpha1- and alpha2 receptors. It is metabolized by CYP3A4 to active and inactive compounds. In the setting of hepatic impairment, there is a 30% reduction in the medication clearance. Half-life of quetiapine in patients with normal hepatic function is roughly 6 hours. Patients with creatinine clearance between 10 and 30 mL/min have a decrease in the clearance of the drug of approximately 25% [99]. Due to its alpha1-antagonist effect, it can cause significant hypotension, which can be an issue in fragile postoperative patients.

Risperidone

Risperidone is available for oral administration in the forms of tablet, orally disintegrated tablet, and oral solution. Risperidone can also be administered intramuscularly in the form of reconstituted suspension. Risperidone has a high 5-HT2 and dopamine D2 receptor antagonist activity. It also antagonizes alpha1, alpha2-adrenergic, and histaminergic receptors. Risperidone has low to moderate affinity for 5-HT1C, 5-HT1D, and 5-HT1A receptors. Risperidone is metabolized mainly by CYP2D6 to 9-hydroxyrisperidone. *N*-dealkylation is a second minor pathway. Risperidone dose needs to be adjusted in renal and hepatic impairment [100].

Lurasidone

Lurasidone is an atypical antipsychotic with mixed serotonin-dopamine antagonist activity. Lurasidone exhibits high affinity for D2, 5-HT2A, and 5-HT7 receptors and moderate affinity for alpha2C-adrenergic receptors and is a partial agonist for 5-HT1A receptors. Lurasidone is available in tablet form. The absorption of lurasidone is increased in the fed state. Lurasidone is metabolized via CYP3A4. It requires dose adjustment in moderate kidney and hepatic impairment. Lurasidone seems to have a minimal impact on QTc prolongation [101].

Antiepileptic Drugs (AEDs)

Gabapentin

Although gabapentin is structurally similar to the neurotransmitter GABA, it does not bind to $GABA_A$ or $GABA_B$ receptors, and it does not appear to influence synthesis or uptake of GABA [102]. High-affinity gabapentin binding sites have been located throughout the brain; these sites correspond to the presence of voltage-gated calcium channels specifically possessing the alpha2-delta-1 subunit [102]. This channel appears to be located presynaptically and may modulate the release of excitatory neurotransmitters which participate in epileptogenesis and nociception. Gabapentin is not metabolized by the liver. It is only 3% protein bound and it lacks significant drug interactions. It was developed as an anticonvulsant, and it has been used as adjunct in the treatment of partial seizures. It has also been used in the treatment of spasticity in multiple sclerosis, amyotrophic lateral sclerosis, postherpetic neuralgia, and moderate to severe primary restless legs syndrome. Gabapentin has also been used in the setting of alcohol withdrawal and dependence, with positive results for decreased cravings and anxiety and improved sleep [103–105]. In addition, it is used for acute and neuropathic pain and can be helpful for treatment of social phobia [106]. Gabapentin is also used for treatment of anxiety [102] and has been suggested for such use in transplant populations, especially when benzodiazepines are to be avoided [69]. However, further studies specific to transplant populations are needed. Due to its renal excretion, gabapentin dose needs adjustment based on creatinine clearance. Additionally, after a 4-hour hemodialysis, a small supplemental dose may be necessary. Side effects include sedation and myoclonus.

Valproic Acid

Valproic acid is approved for the treatment of different seizure types, prophylaxis for migraine, and management of mania associated with bipolar disorder. It has also been used for delirium management [107]. Valproic acid undergoes extensive hepatic metabolism mainly via glucuronide conjugation, mitochondrial beta-oxidation, and in lesser extent oxidation by CYP2C9, CYP2C19, and CYP2A6 [108]. Protein binding is 80–90% and dependent on drug concentration. Half-life elimination is 9–19 hours in adults [108]. Valproic acid does not need dose adjustment in renal impairment; however, monitoring of free fraction of the drug instead of the total fraction is more appropriate, given that in kidney disease protein binding decreases. The use of valproic acid is not recommended in patients with liver impairment due to decreased clearance and the risk of hepatotoxicity. Hepatic disease is also associated with decreased albumin concentrations and increase in the free drug fraction. Free instead of total concentrations of valproic acid should be monitored in liver impairment, if the medication is indeed used in this setting [109]. Other conditions that lead to increased free fraction of the drug are cachexia and elevated free fatty acids. Elevated free fraction increases risk of lethargy and cognitive slowing. Of note, valproic acid is decreased by 80% when combined with carbapenems [108]. Other undesirable side effects for the transplant patients include thrombocytopenia and platelet dysfunction; hence, close monitoring is needed [110]. Moreover, valproic acid

carries a black box warning against life-threatening pancreatitis. It is contraindicated in pregnancy due to significant risk of congenital malformations, such as neural tube defects, and decreased intelligence quotient (IQ) scores in offspring.

Carbamazepine

Carbamazepine has multiple properties including anticonvulsant, anticholinergic, antineuralgic, antidiuretic, muscle relaxant, mood stabilizing, and antiarrhythmic. Carbamazepine is metabolized via CYP3A4 to an active metabolite. Carbamazepine is considered a potent inducer of CYP3A4 (autoinduction). Given that immunosuppressants are for the most part metabolized by this isozyme, the concurrent use of carbamazepine will likely reduce their levels risking rejection. As carbamazepine is an autoinductor, its half-life is variable for the first 3–5 weeks after initiation of a fixed carbamazepine dose. In addition to drug-drug interactions with immunosuppressants, another problematic aspect of carbamazepine use in transplant patients is the risk for leukopenia and blood dyscrasias, such as aplastic anemia and agranulocytosis [110]. Carbamazepine can alter bone metabolism and vitamin D levels. Carbamazepine should be used with caution in hepatic impairment, and it may require discontinuation if liver function worsens or dysfunction becomes apparent. It requires dose adjustment in renal impairment.

Oxcarbazepine

Compared to carbamazepine, oxcarbazepine is not associated with blood dyscrasias. It is a weak inducer of CYP3A4 but can still decrease immunosuppressant levels. It has also been associated with decreased vitamin D levels. Autoinduction has not been observed. Oxcarbazepine is metabolized in the liver to an active compound. Oxcarbazepine is a dose-dependent CYP2C19 inhibitor. Hyponatremia is a common side effect. Oxcarbazepine has not been studied in severe hepatic impairment. In renal impairment the clearance of the active metabolite changes from approximately 9 hours to 19 hours.

Topiramate

Besides its uses in the treatment of several types of seizures and migraine prophylaxis, topiramate continues to be studied as adjunctive therapy for bipolar disorder. It also has emerging evidence for treatment of alcohol dependence [111]. Topiramate is not extensively metabolized, with nearly 70% of the dose being eliminated by the kidney unchanged. Topiramate requires adjustment for renal impairment and an added post-dialysis dose. It should be used with caution in hepatic impairment given that its clearance can be reduced. Overall, due to its side effects, including cognitive dysfunction, topiramate is not desirable in patients receiving potentially neurotoxic medications such as CNIs.

Lithium

Lithium is available in oral form. Lithium is approved for the treatment of manic episodes and as maintenance treatment for bipolar I disorder. Lithium is also effective as an adjunct for refractory depression and for reducing the risk of suicide in patients with mood disorders [96]. Lithium is not metabolized by liver and is eliminated solely by the kidney [96]. It has minimal protein binding of 15%. Dose needs to be adjusted according to creatinine clearance and dialysis status. Its half-life elimination in adults is 18–36 hours. Lithium clearance is affected by kidney function as well as by hyponatremia, hypernatremia, diuretic use, and dehydration [112]. Potential electrolyte changes and fluid shifts in transplant patients and the potential concurrent use with sodium-depleting diuretics, especially thiazides and angiotensin-converting enzyme inhibitors, make the safe use of lithium challenging in the post-transplant patient, particularly early after surgery. Lithium can cause adverse effects in the heart, believed to be related to intracellular hypokalemia and extracellular hyperkalemia imbalance that can give rise to cardiac arrest. It can also cause nephrotoxicity, tremors, weight gain, and cognitive slowing, all potential side effects of commonly used immunosuppressants. Therefore, the use of lithium in the late post-transplant patient needs to be carefully considered using the best clinical judgment and individualized approach based on the patient's history.

Medications Used in the Treatment of Substance Use Disorders

Acamprosate

Acamprosate appears to increase the activity of the GABAergic system, and decreases activity of glutamate within the CNS, including a decrease in activity at N-methyl D-aspartate (NMDA) receptors. Acamprosate may affect CNS calcium channels. Acamprosate does not undergo hepatic metabolism and is eliminated unchanged via the kidneys. It requires dose adjustment in renal impairment, and it is contraindicated when creatinine clearance is lower than 30% [113].

Disulfiram

Disulfiram interferes with the hepatic oxidation of acetaldehyde, which leads to its accumulation and unpleasant symptoms if the patient ingests ethanol. Symptoms include throbbing headache and neck, dyspnea, vomiting, diaphoresis, thirst, chest pain, palpitations, hypotension, blurred vision, vertigo, weakness, anxiety, syncope, and confusion. Cardiac collapse and deaths have been reported [114, 115]. Disulfiram has also been associated with rare cases of fulminant hepatic failure, and liver transplantation in such a patient has been reported [116]. Due to multiple potential interac-

tions with other drugs, disulfiram is not recommended in transplant patients.

Naltrexone

Naltrexone is an opioid antagonist used to help maintain an opioid-free state in patients with opioid use disorders and in the management of patients with alcohol use disorder, decreasing the cravings, alcohol use, and alcohol relapse. Naltrexone is associated with increased risk for hepatotoxicity [117]. The CYP system is not involved in the metabolism of naltrexone. Dose adjustment may be necessary in hepatic and renal impairment. Naltrexone needs to be discontinued when pain control requires opioid agonists, such as prior or after surgical procedures.

Methadone

Methadone is an opioid agonist used in the maintenance of opioid use disorder [118, 119]. It undergoes hepatic metabolism via CYP3A4, CYP2D6, CYP2B6, CYP2C19, and CYP2C9 and is a substrate of P-glycoprotein [119]. It requires dose adjustment in severe renal impairment and caution is needed in hepatic impairment. Methadone can prolong QTc, and thus monitoring is required [118]. Methadone half-life varies between 8 hours and 59 hours in adults. Management of pain postoperatively can be accomplished by continuing the pre-transplant methadone dose and adding another opioid temporarily or increasing the pre-transplant methadone dose. With chronic use, methadone can autoinduce its metabolism. Please see Chap. 45 on further discussion of methadone in transplant patients.

Buprenorphine

Buprenorphine is a semisynthetic mixed opioid agonist-antagonist. It has a ceiling effect which may make it comparatively safer than full opioid agonists [119]. It is metabolized by CYP3A4. See Chap. 45 on further discussion of buprenorphine in transplant patients.

Alpha2 Agonists

Dexmedetomidine

Dexmedetomidine is a selective alpha$_2$-adrenoceptor agonist with sympatholytic, sedative, and analgesic effects, similar to clonidine. Intravenous dexmedetomidine drips are used in intensive care settings for the management of sedation in patients requiring ventilatory support or periprocedurally. It has been shown to decrease risk of delirium in ICU populations, as compared to other sedative drips, such as propofol or benzodiazepines [120, 121].

Protective neurocognitive effects in orthotopic liver transplantation are being studied with encouraging results; however, further research is needed [122]. Dexmedetomidine undergoes hepatic metabolism via N-glucuronidation, N-methylation, and CYP2A6. Its elimination half-life is 2 hours. Although no dose adjustment is recommended in kidney impairment, dose reduction should be considered in hepatic impairment as the clearance is reduced in varying degrees based on the level of impairment. Dexmedetomidine can cause bradycardia and lower blood pressure.

Conclusions

Transplant recipients are at increased risk for cognitive, anxiety, and mood disorders; thus they may require treatment with a variety of psychopharmacological agents. Clinicians should be aware of neuropsychiatric side effects of medications used in transplant recipients, pharmacodynamics and pharmacokinetics of psychotropic agents in patients with end-stage organ disease and post-transplant, and drug-drug interactions. Some general guidelines are summarized below:

- Most immunosuppressant agents are substrates of CYP3A4; hence, attention needs to be given to the multiple potential interactions with psychiatric medications.
- In general, start psychiatric medications at a low dose and titrate slowly while monitoring for potential side effects and drug-drug interactions.
- Monitor for recent changes of concurrent medications, as additions or discontinuations may alter the metabolism of the remaining medications, and adjust accordingly.
- CNIs are nephrotoxic, and mTOR inhibitors can cause kidney function alterations; hence, close monitoring and adjustment of psychiatric medications such as lithium and gabapentin may become necessary.
- Discontinue medications when they are no longer needed and caution patients and team members of the potential consequences of introduced changes as well as the signs and symptoms that need to be monitored.
- Inquire about all medications the patient is taking, including herbal supplements.
- Avoid starting new medications in a long-acting form if possible. This will allow rapid withdrawal of the medication in case of intolerable side effects.

References

1. Dew MA, DiMartini AF, DeVito Dabbs AJ, Fox KR, Myaskovsky L, Posluszny DM, et al. Onset and risk factors for anxiety and depression during the first 2 years after lung transplantation. Gen Hosp Psychiatry. 2012;34(2):127–38.
2. Dew MA, Kormos RL, DiMartini AF, Switzer GE, Schulberg HC, Roth LH, et al. Prevalence and risk of depression and anxiety-

related disorders during the first three years after heart transplantation. Psychosomatics. 2001;42(4):300–13.
3. Dew MA, Rosenberger EM, Myaskovsky L, DiMartini AF, DeVito Dabbs AJ, Posluszny DM, et al. Depression and anxiety as risk factors for morbidity and mortality after organ transplantation: a systematic review and meta-analysis. Transplantation. 2015;100(5):988–1003.
4. Smith PJ, Rivelli S, Waters A, Reynolds J, Hoyle A, Flowers M, et al. Neurocognitive changes after lung transplantation. Ann Am Thorac Soc. 2014;11(10):1520–7.
5. Smith PJ, Rivelli SK, Waters AM, Hoyle A, Durheim MT, Reynolds JM, et al. Delirium affects length of hospital stay after lung transplantation. J Crit Care. 2015;30(1):126–9.
6. Basinski JR, Alfano CM, Katon WJ, Syrjala KL, Fann JR. Impact of delirium on distress, health-related quality of life, and cognition 6 months and 1 year after hematopoietic cell transplant. Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant. [Clinical Trial Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. 2010;16(6):824–31.
7. DiMartini A, Crone C, Fireman M, Dew MA. Psychiatric aspects of organ transplantation in critical care. Crit care Clin. [Research Support, N.I.H., Extramural Review]. 2008;24(4):949–81, x.
8. Rang H, Ritter R, Flower RJ, Rang GH. Drug metabolism and elimination. Rang and Dale's pharmacology. Livingstone: Elsevier Churchill; 2016. p. 116–24.
9. Enright EF, Gahan CG, Joyce SA, Griffin BT. The Impact of the Gut Microbiota on Drug Metabolism and Clinical Outcome. Yale J Biol Med. [Review Research Support, Non-U.S. Gov't]. 2016;89(3):375–82.
10. Klaassen CD, Cui JY. Review: mechanisms of how the intestinal microbiota alters the effects of drugs and bile acids. Drug Metab Dispos Biol Fate Chem. [Research Support, N.I.H., Extramural Review]. 2015;43(10):1505–21.
11. Dreisbach AW, Lertora JJ. The effect of chronic renal failure on hepatic drug metabolism and drug disposition. Semin Dial. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S. Review]. 2003;16(1):45–50.
12. Holford NG. Pharmacokinetics & pharmacodynamics: rational dosing & the time course of drug action. In: Katzung BG, Trevor AJ, editors. Basic and clinical pharmacology. 13th ed. New York: McGraw-Hill; 2015.
13. Lake DF, Briggs AD. Immunopharmacology. In: Katzung BG, Trevor AJ, editors. Basic and clinical pharmacology. 13th ed. New York: McGraw-Hill; 2015.
14. Muller J, Keiser M, Drozdzik M, Oswald S. Expression, regulation and function of intestinal drug transporters: an update. Biol Chem. [Review Research Support, Non-U.S. Gov't]. 2017;398(2):175–92.
15. Levitsky J, Goldberg D, Smith AR, Mansfield SA, Gillespie BW, Merion RM, et al. Acute rejection increases risk of graft failure and death in recent liver transplant recipients. Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc. [Observational Study]. 2017;15(4):584–93e2.
16. Fireman M, DiMartini A, Crone C. Organ transplantation. In: Ferrando S, Levenson JL, Owen JA, editors. Clinical manual of psychopharmacology in medically ill. Arlington: American Psychiatric Publishing; 2010. p. 597–631.
17. Wu GS, Cruz RJ Jr, Cai JC. Acute antibody-mediated rejection after intestinal transplantation. World J Transplant. 2016;6(4): 719–28.
18. Lake J. Liver transplantation. In: Friedman S, editor. Current diagnosis and treatmetn in gastroenterology. New York: McGraw-Hill; 2003. p. 813–34.
19. Fireman M, DiMartini AF, Armstrong SC, Cozza KL. Immunosuppressants. Psychosomatics. [Review]. 2004;45(4): 354–60.
20. Wynn G. Transplant surgery and rheumatology. Immunosuppressants. In: Wynn G, Oesterheld J, Gozza K, Armstrong S, editors. Clinical manual of drug interaction principles for medical practice. Washingon, DC: American Psychiatric Publishing, Inc.; 2009. p. 461–72.
21. Dubovsky AN, Arvikar S, Stern TA, Axelrod L. The neuropsychiatric complications of glucocorticoid use: steroid psychosis revisited. Psychosomatics. [Review]. 2012;53(2):103–15.
22. Wolkowitz OM. Long-lasting behavioral changes following prednisone withdrawal. JAMA. [Case Reports Letter]. 1989;261(12):1731–2.
23. Fardet L, Nazareth I, Whitaker HJ, Petersen I. Severe neuropsychiatric outcomes following discontinuation of long-term glucocorticoid therapy: a cohort study. J Clin Psychiatry. 2013;74(4):e281–6.
24. West S, Kenedi C. Strategies to prevent the neuropsychiatric side-effects of corticosteroids: a case report and review of the literature. Curr Opin Organ Transplant.. [Case Reports Review]. 2014;19(2):201–8.
25. Goldman LS, Goveas J. Olanzapine treatment of corticosteroid-induced mood disorders. Psychosomatics. [Case Reports]. 2002;43(6):495–7.
26. Roxanas MG, Hunt GE. Rapid reversal of corticosteroid-induced mania with sodium valproate: a case series of 20 patients. Psychosomatics. 2012;53(6):575–81.
27. Viswanathan R, Glickman L. Clonazepam in the treatment of steroid-induced mania in a patient after renal transplantation. N Engl J Med.. [Case Reports Letter]. 1989;320(5):319–20.
28. Sun X, Wu Y, Chen B, Zhang Z, Zhou W, Tong Y, et al. Regulator of calcineurin 1 (RCAN1) facilitates neuronal apoptosis through caspase-3 activation. J Biol Chem. [Research Support, Non--U.S. Gov't]. 2011;286(11):9049–62.
29. Trzepacz PT, DiMartini A, Tringali R. Psychopharmacologic issues in organ transplantation. Part I: Pharmacokinetics in organ failure and psychiatric aspects of immunosuppressants and anti-infectious agents. Psychosomatics. [Review]. 1993;34(3):199–207.
30. Song T, Rao Z, Tan Q, Qiu Y, Liu J, Huang Z, et al. Calcineurin inhibitors associated posterior reversible encephalopathy syndrome in solid organ transplantation: report of 2 cases and literature review. Medicine. [Case Reports Research Support, Non-U.S. Gov't Review]. 2016;95(14):e3173.
31. Rosso L, Nosotti M, Mendogni P, Palleschi A, Tosi D, Montoli M, et al. Lung transplantation and posterior reversible encephalopathy syndrome: a case series. Transplant Proc. 2012;44(7): 2022–5.
32. Smith PJ, Stonerock GL, Ingle KK, Saulino CK, Hoffman B, Wasserman B, et al. Neurological sequelae and clinical outcomes after lung transplantation. Transplant Direct. 2018;4(4):e353.
33. Chen S, Hu J, Xu L, Brandon D, Yu J, Zhang J. Posterior reversible encephalopathy syndrome after transplantation: a review. Mol Neurobiol. [Review]. 2016;53(10):6897–909.
34. Schusse CM, Peterson AL, Caplan JP. Posterior reversible encephalopathy syndrome. Psychosomatics. [Case Reports Review]. 2013;54(3):205–11.
35. Hayes D Jr, Adler B, Turner TL, Mansour HM. Alternative tacrolimus and sirolimus regimen associated with rapid resolution of posterior reversible encephalopathy syndrome after lung transplantation. Pediatr Neurol. [Case Reports]. 2014;50(3):272–5.
36. Curtis JJ, Jones P, Barbeito R. Large within-day variation in cyclosporine absorption: circadian variation or food effect? Clin J Am Soc Nephrol CJASN. [Research Support, Non-U.S. Gov't]. 2006;1(3):462–6.
37. Aronson J. Meyler's side effects of herbal medicines. Amsterdam: Elsevier Science; 2008.
38. Finsterer J, Ohnsorge P. Influence of mitochondrion-toxic agents on the cardiovascular system. Regul Toxicol Pharmacol RTP [Review]. 2013;67(3):434–45.

39. Hodak SP, Moubarak JB, Rodriguez I, Gelfand MC, Alijani MR, Tracy CM. QT prolongation and near fatal cardiac arrhythmia after intravenous tacrolimus administration: a case report. Transplantation. [Case Reports Research Support, Non--U.S. Gov't]. 1998;66(4):535–7.
40. Ikitimur B, Cosansu K, Karadag B, Cakmak HA, Avci BK, Erturk E, et al. Long-term impact of different immunosuppressive drugs on QT and PR intervals in renal transplant patients. Ann Noninvasive Electrocardiol Off J Int Soc Holter Noninvasive Electrocardiol Inc. 2015;20(5):426–32.
41. Beach SR, Celano CM, Noseworthy PA, Januzzi JL, Huffman JC. QTc prolongation, torsades de pointes, and psychotropic medications. Psychosomatics. [Review]. 2013;54(1):1–13.
42. Bradley J, Watson C. mTOR inhibitors: Sirolimus and everolimus. In: Morris P, Knechtle S, editors. Kidney transplantation: principles and practice. London: Elsevier Health Sciences; 2014. p. 267–86.
43. Atgam (lymphocyte immune globulin, antithymocyte globulin [equine]) [prescribing information]. New York: Pfizer, Inc; 2015.
44. Thymoglobulin (antithymocyte glbolung [rabbit] package insert. Cambridge, MA: Genzyme Corportaion; 2016.
45. Simulect (basiliximab) package insert. East Hanover: Novartis Pharmaceuticals Corporation; 2005.
46. Campath (alemtuzumab) package insert. Cambridge, MA: Genzyme Corporation; 2014.
47. Lemtrada (alemtuzumab) injection package insert. Camridge, MA: Genzyme Corporation; 2017.
48. Rituxan (rituximab) package insert. South San Francisco: Genentech, Inc.; 2013.
49. Myfortic (mycophenolate sodium) [prescribing information]. East Hanover: Novartis Pharmaceuticals Corporation; 2015.
50. Azathioprine.Lexicomp Online®, Lexi-Drugs. Hudson: Lexi-Comp, Inc.; 2017.
51. Gruessner A, Jie T, Papas K, Porubsky M, Rana A, Smith M, et al. Transplantation. In: Bruncardi F, Andersen D, Billiar T, Dunn D, Hunter J, Matthews J, et al., editors. Schwartz's principles of surgery. New York: McGraw-Hill; 2015.
52. O'Connor CM, Jiang W, Kuchibhatla M, Silva SG, Cuffe MS, Callwood DD, et al. Safety and efficacy of sertraline for depression in patients with heart failure: results of the SADHART-CHF (Sertraline against depression and heart disease in chronic heart failure) trial. J Am Coll Cardiol. [Randomized Controlled Trial Research Support, N.I.H., Extramural]. 2010;56(9):692–9.
53. Kalender B, Ozdemir AC, Yalug I, Dervisoglu E. Antidepressant treatment increases quality of life in patients with chronic renal failure. Ren Fail. 2007;29(7):817–22.
54. Gottlieb SS, Kop WJ, Thomas SA, Katzen S, Vesely MR, Greenberg N, et al. A double-blind placebo-controlled pilot study of controlled-release paroxetine on depression and quality of life in chronic heart failure. Am Heart J. [Randomized Controlled Trial Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, Non-P.H.S.]. 2007;153(5):868–73.
55. Jeong BO, Kim SW, Kim SY, Kim JM, Shin IS, Yoon JS. Use of serotonergic antidepressants and bleeding risk in patients undergoing surgery. Psychosomatics. [Review]. 2014;55(3):213–20.
56. Eckersley MJ, Sepehripour AH, Casula R, Punjabi P, Athanasiou T. Do selective serotonin reuptake inhibitors increase the risk of bleeding or mortality following coronary artery bypass graft surgery? A meta-analysis of observational studies. Perfusion. 2018;1:267659118765933.
57. Varela Pinon M, Adan-Manes J. Selective Serotonin reuptake inhibitor-induced hyponatremia: clinical implications and therapeutic alternatives. Clin Neuropharmacol. [Case Reports]. 2017;40(4):177–9.
58. De Picker L, Van Den Eede F, Dumont G, Moorkens G, Sabbe BG. Antidepressants and the risk of hyponatremia: a class-by-class review of literature. Psychosomatics. [Review]. 2014;55(6):536–47.
59. Tsapakis EM, Gamie Z, Tran GT, Adshead S, Lampard A, Mantalaris A, et al. The adverse skeletal effects of selective serotonin reuptake inhibitors. Eur Psychiatry J Assoc Eur Psychiatr. [Review]. 2012;27(3):156–69.
60. Sher Y, Zimbrean P. Psychiatric aspects of organ transplantation in critical care: an update. Crit Care Clin. [Review]. 2017;33(3):659–79.
61. DeBattista C. Antidepressant agents. In: Katzung B, Trevor A, editors. Basic and clinical pharmacology. New York: McGraw-Hill; 2015.
62. Crewe HK, Lennard MS, Tucker GT, Woods FR, Haddock RE. The effect of selective serotonin re-uptake inhibitors on cytochrome P4502D6 (CYP2D6) activity in human liver microsomes. Br J Clin Pharmacol. [Comparative Study]. 1992;34(3):262–5.
63. Ozdemir V, Naranjo CA, Herrmann N, Shulman RW, Sellers EM, Reed K, et al. The extent and determinants of changes in CYP2D6 and CYP1A2 activities with therapeutic doses of sertraline. J ClinPsychopharmacol. [Comparative Study Research Support, Non-U.S. Gov't]. 1998;18(1):55–61.
64. Preskorn SH, Alderman J, Greenblatt DJ, Horst WD. Sertraline does not inhibit cytochrome P450 3A-mediated drug metabolism in vivo. Psychopharmacol Bull [Comparative Study]. 1997;33(4):659–65.
65. Lill J, Bauer LA, Horn JR, Hansten PD. Cyclosporine-drug interactions and the influence of patient age. Am J Health Syst Pharm AJHP Off J Am Soc Health Syst Pharm. [Research Support, Non--U.S. Gov't]. 2000;57(17):1579–84.
66. Mayo MJ, Handem I, Saldana S, Jacobe H, Getachew Y, Rush AJ. Sertraline as a first-line treatment for cholestatic pruritus. Hepatology. [Randomized Controlled Trial Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. 2007;45(3):666–74.
67. Smoller JW, Pollack MH, Systrom D, Kradin RL. Sertraline effects on dyspnea in patients with obstructive airways disease. Psychosomatics. [Case Reports]. 1998;39(1):24–9.
68. Yalcin AU, Sahin G, Erol M, Bal C. Sertraline hydrochloride treatment for patients with hemodialysis hypotension. Blood Purif. [Clinical Trial]. 2002;20(2):150–3.
69. Crone CC, Gabriel GM. Treatment of anxiety and depression in transplant patients: pharmacokinetic considerations. Clin Pharmacokinet. [Comparative Study Review]. 2004;43(6):361–94.
70. Sandson NB, Armstrong SC, Cozza KL. An overview of psychotropic drug-drug interactions. Psychosomatics. [Review]. 2005;46(5):464–94.
71. FDA Drug Safety Communication: revised recommendations for Celexa (citalopram hydrobromide) related to a potential risk of abnormal heart rhythms with high doses. U.S. Food and Drug Administration; 2012 [cited 2018 5/14/2018]; Available from: https://www.fda.gov/Drugs/DrugSafety/ucm297391.htm.
72. Gerlach LB, Kales HC, Maust DT, Chiang C, Stano C, Choe HM, et al. Unintended consequences of adjusting citalopram prescriptions following the 2011 FDA warning. Am J Geriatr Psychiatry Off J Am Assoc Geriatr Psychiatry. 2017;25(4):407–14.
73. Newey CR, Khawam E, Coffman K. Two cases of serotonin syndrome with venlafaxine and calcineurin inhibitors. Psychosomatics. [Case Reports]. 2011;52(3):286–90.
74. Desvenlafaxine. Lexicomp® Online, Lexi-Drugs. Hudson: Lexi-Comp, Inc; [cited 2017 28 Dec]; Available from: https://online.lexi.com.
75. Voican CS, Corruble E, Naveau S, Perlemuter G. Antidepressant-induced liver injury: a review for clinicians. Am J Psychiatry. [Review]. 2014;171(4):404–15.
76. Wernicke J, Pangallo B, Wang F, Murray I, Henck JW, Knadler MP, et al. Hepatic effects of duloxetine-I: non-clinical and clinical

trial data. Curr Drug Saf. [Research Support, Non-U.S. Gov't Review]. 2008;3(2):132–42.
77. Hartmann PM. Mirtazapine: a newer antidepressant. Am Fam Physician. [Review]. 1999;59(1):159–61.
78. Jamilloux Y, Kerever S, Ferry T, Broussolle C, Honnorat J, Seve P. Treatment of progressive multifocal Leukoencephalopathy With Mirtazapine. Clin Drug Investig. [Review]. 2016;36(10):783–9.
79. Boinpally R, Alcorn H, Adams MH, Longstreth J, Edwards J. Pharmacokinetics of vilazodone in patients with mild or moderate renal impairment. Clin Drug Investig. [Clinical Trial, Phase I Research Support, Non-U.S. Gov't]. 2013;33(3):199–206.
80. Owen JR, Nemeroff CB. New antidepressants and the cytochrome P450 system: focus on venlafaxine, nefazodone, and mirtazapine. Depress Anxiety. [Research Support, U.S. Gov't, P.H.S. Review]. 1998;7(Suppl 1):24–32.
81. Nefazodone hydrochloride tablet package insert. Jacksonville: Ranbaxy Pharmaceutical Inc.; 2008.
82. Livingston MG, Livingston HM. Monoamine oxidase inhibitors. An update on drug interactions. Drug Saf. [Review]. 1996;14(4):219–27.
83. Borrelli F, Izzo AA. Herb-drug interactions with St John's wort (Hypericum perforatum): an update on clinical observations. AAPS J. [Review]. 2009;11(4):710–27.
84. Moschella C, Jaber BL. Interaction between cyclosporine and Hypericum perforatum (St. John's wort) after organ transplantation. Am J kidney Dis Off J Natl Kidney Found. [Case Reports]. 2001;38(5):1105–7.
85. Turton-Weeks SM, Barone GW, Gurley BJ, Ketel BL, Lightfoot ML, Abul-Ezz SR. St John's wort: a hidden risk for transplant patients. Prog Transplant. [Case Reports]. 2001;11(2):116–20.
86. Hardy SE. Methylphenidate for the treatment of depressive symptoms, including fatigue and apathy, in medically ill older adults and terminally ill adults. Am J Geriatr Pharmacother. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Review]. 2009;7(1):34–59.
87. FDA Drug Safety Communication: safety review update of medications used to treat attention-deficit/hyperactivity disorder (ADHD) in children and young adults. U.S. Food & Drug Administration2011 [cited 2018 May 13]; Available from: https://www.fda.gov/Drugs/DrugSafety/ucm277770.htm.
88. Plutchik L, Snyder S, Drooker M, Chodoff L, Sheiner P. Methylphenidate in post liver transplant patients. Psychosomatics. [Case Reports]. 1998;39(2):118–23.
89. Tomlinson D, Robinson PD, Oberoi S, Cataudella D, Culos-Reed N, Davis H, et al. Pharmacologic interventions for fatigue in cancer and transplantation: a meta-analysis. Curr Oncol. [Review]. 2018;25(2):e152–e67.
90. Corchs F, Teng CT. Amphetamine, catatonic depression, and heart transplant: a case report. Revista Bras Psiquiatr. [Case Reports Letter]. 2010;32(3):324–6.
91. Tong HY, Diaz C, Collantes E, Medrano N, Borobia AM, Jara P, et al. Liver transplant in a patient under methylphenidate therapy: a case report and review of the literature. Case Rep Pediatr. 2015;2015:437298.
92. Dextroamphetamine. Clinical Key [cited 2018 Jan 4]; Available from: http://www.clinicalkey.com.
93. Murillo-Rodriguez E, Barciela Veras A, Barbosa Rocha N, Budde H, Machado S. An overview of the clinical uses, pharmacology, and safety of Modafinil. ACS Chem Neurosci. [Research Support, Non-U.S. Gov't]. 2018;9(2):151–8.
94. Desai HD, Seabolt J, Jann MW. Smoking in patients receiving psychotropic medications: a pharmacokinetic perspective. CNS Drugs. [Review]. 2001;15(6):469–94.
95. Eison AS, Temple DL, Jr. Buspirone: review of its pharmacology and current perspectives on its mechanism of action. Am J Med. [Review]. 1986;80(3B):1–9.
96. Meltzer H. Antipsychotic agents & lithium. In: Katzung B, Trevor A, editors. Basic and clinical pharmacology. New York: McGraw-Hill; 2015.
97. de Bartolomeis A, Tomasetti C, Iasevoli F. Update on the Mechanism of Action of Aripiprazole: Translational Insights into Antipsychotic Strategies Beyond Dopamine Receptor Antagonism. CNS Drugs. [Research Support, Non-U.S. Gov't Review]. 2015;29(9):773–99.
98. Zyprexa (olanzapine, all formulations) package insert. Indianapolis: Eli Lilly and company; 2017.
99. Quetiapine. [cited 2018 Jan 5]; Available from: http://clinicalkey.com.
100. Risperidone. Lexicomp Online ®. Lexi-drugs®. Hudson: Lexicomp, Inc; [cited 2018 Jan 5].
101. Citrome L. A review of the pharmacology, efficacy and tolerability of recently approved and upcoming oral antipsychotics: an evidence-based medicine approach. CNS Drugs. [Review]. 2013;27(11):879–911.
102. Greenblatt HK, Greenblatt DJ. Gabapentin and pregabalin for the treatment of anxiety disorders. Clinical Pharmacol Drug Dev. [Editorial]. 2018;7(3):228–32.
103. Leung JG, Hall-Flavin D, Nelson S, Schmidt KA, Schak KM. The role of gabapentin in the management of alcohol withdrawal and dependence. Ann Pharmacother. [Review]. 2015;49(8):897–906.
104. Leung JG, Rakocevic DB, Allen ND, Handler EM, Perossa BA, Borreggine KL, et al. Use of a gabapentin protocol for the Management of Alcohol Withdrawal: a preliminary experience expanding from the consultation-liaison psychiatry service. Psychosomatics. 2018;21
105. Maldonado JR. Novel Algorithms for the Prophylaxis and Management of Alcohol Withdrawal Syndromes-Beyond Benzodiazepines. Criti Care Clin. [Review]. 2017;33(3):559–99.
106. Pande AC, Davidson JR, Jefferson JW, Janney CA, Katzelnick DJ, Weisler RH, et al. Treatment of social phobia with gabapentin: a placebo-controlled study. J Clin Psychopharmacol. [Clinical Trial Multicenter Study Randomized Controlled Trial Research Support, Non-U.S. Gov't]. 1999;19(4):341–8.
107. Sher Y, Miller AC, Lolak S, Ament A, Maldonado JR. Adjunctive valproic acid in management-refractory hyperactive delirium: a case series and rationale. J Neuropsychiatr Clin Neurosci. 2015:appineuropsych14080190.
108. Sher Y, Miller Cramer AC, Ament A, Lolak S, Maldonado JR. Valproic acid for treatment of hyperactive or mixed delirium: rationale and literature review. Psychosomatics. [Review]. 2015;56(6):615–25.
109. Haroldson JA, Kramer LE, Wolff DL, Lake KD. Elevated free fractions of valproic acid in a heart transplant patient with hypoalbuminemia. Ann Pharmacother. [Case Reports]. 2000;34(2):183–7.
110. Verrotti A, Scaparrotta A, Grosso S, Chiarelli F, Coppola G. Anticonvulsant drugs and hematological disease. Neurol Sci Off J Ital Neurol Soc Ital Soc Clin Neurophysiol. [Review]. 2014;35(7):983–93.
111. Guglielmo R, Martinotti G, Quatrale M, Ioime L, Kadilli I, Di Nicola M, et al. Topiramate in alcohol use disorders: review and update. CNS Drugs. [Review]. 2015;29(5):383–95.
112. DasGupta K, Jefferson JW. The use of lithium in the medically ill. Gen Hosp Psychiatry. [Review]. 1990;12(2):83–97.
113. Acamprosate [prescribing information]. Morgantown: Mylan Pharmaceuticals Inc; 2015.
114. Moreels S, Neyrinck A, Desmet W. Intractable hypotension and myocardial ischaemia induced by co-ingestion of ethanol and disulfiram. Acta Cardiol. [Case Reports]. 2012;67(4):491–3.
115. Jeronimo A, Meira C, Amaro A, Campello GC, Granja C. Cardiogenic shock caused by disulfiram. Arq Bras Cardiol. [Case Reports]. 2009;92(3):e16–8.

116. Mohanty SR, LaBrecque DR, Mitros FA, Layden TJ. Liver transplantation for disulfiram-induced fulminant hepatic failure. J Clin Gastroenterol. [Case Reports Review]. 2004;38(3):292–5.
117. Garbutt JC. Efficacy and tolerability of naltrexone in the management of alcohol dependence. Curr Pharm Des [Review]. 2010;16(19):2091–7.
118. Westermeyer J, Adabag S, Anand V, Thuras P, Yoon G, Batres YCT. Methadone maintenance dose/weight ratio, long QTc, and EKG screening. Am J Addict. 2016;25(6):499–507.
119. Schumacher M, Basbaum A, Way W. Opioid analgesics & antagonists. In: Katzung B, Trevor A, editors. Basic and clinical pharmacology. New Yok: McGraw-Hill; 2015.
120. Xia ZQ, Chen SQ, Yao X, Xie CB, Wen SH, Liu KX. Clinical benefits of dexmedetomidine versus propofol in adult intensive care unit patients: a meta-analysis of randomized clinical trials. J Surg Res. [Comparative Study Meta-Analysis Research Support, Non--U.S. Gov't Review]. 2013;185(2):833–43.
121. Maldonado JR, Wysong A, van der Starre PJ, Block T, Miller C, Reitz BA. Dexmedetomidine and the reduction of postoperative delirium after cardiac surgery. Psychosomatics. 2009;50(3):206–17.
122. Xu G, Li LL, Sun ZT, Zhang W, Han XP. Effects of Dexmedetomidine on postoperative cognitive dysfunction and serum levels of b-amyloid and neuronal microtubule-associated protein in orthotopic liver transplantation patients. Ann transplant. [Randomized Controlled Trial]. 2016;21:508–15.