The Renal Dialysis and Kidney Transplant Patient

28

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Contents

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28.1 Introduction

Kidney disease is widespread and endemic. It is estimated in its latest available statistics that 27 million people in the US have chronic kidney disease (United States Renal Data System 2012). Its extreme form, renal failure (ESRD) is diagnosed in 117,000 people in the US yearly.

There are 86,000 people in the US waiting for a kidney transplant and 355,000 on form for dialysis. Medicare is the major payer for treatment of renal failure in the US for which it spends $47.5 billion yearly. Therefore, the treatment of renal failure is a major part of American medicine. In order for the behaviorally trained professional to make any depth impact in the study and/or treatment of these patients, he/she must have a working relationship with the nephrology staff (Levenson and Olbrisch 1993). Contact starts at the top of the nephrology/transplant surgery chain of command. If the relationship is to be anything more than an outside specialist rendering judgment, it is essential that one be accepted by the director of nephrology/transplant surgery as a member of the team (Cohen et al. 2005a). If so, then there may be a possibility for a true liaison relationship to develop. If not, then the relationship is most likely constrained to a limited consolatory one. Lest one be too optimistic about entering such a relationship, one needs to be reminded that, in general, resistance and at times hostility toward a behavioral view surrounding

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physical illnesses and their treatments can and often are great among physicians (Reichsman and Levy 1972).

There is a good body of research and clinical experience about the behavioral aspects of dialysis and renal transplantation because the kidney is the first vital organ that has been transplanted and the first for which there is a mechanism for its artificial substitution by dialysis. Nevertheless there is still a dearth of systematic, mutlisite studies. With these shortcomings in mind, the authors of this chapter will endeavor to tell the reader what are their major stresses, their various forms of treatment, the psychological problems of these patients and how the behaviorally trained professional may help these patients.

28.2 Forms of Dialysis and Stresses and Their Treatment

There are two forms of dialysis, hemodialysis and peritoneal dialysis. In the former, the patient's blood is delivered into the dialysis machine and separated from dialysis fluid via a semipermeable membrane. The processes of dialysis is an osmotic one in which compounds flow through a semipermeable membrane from the higher concentration side into the side of the membrane with a lower concentration of those substances. For example, if the ionic concentration of potassium is lower in the dialysate fluid than in the patient's blood, potassium will flow from the blood through the membrane and into the dialysate fluid (Parker 1992). In peritoneal dialysis, dialysis fluid is delivered via an abdominal fistula directly into the peritoneal cavity and the peritoneum serves as the semipermeable membrane. Careful consideration is given to what constitutes dialysis fluid. Of course, water is its main constituent. The selection of substances in the water involves a molecular size small enough to go through the membrane and substances that need to be removed and others replaced.

Dialysis, more so than any other form of medical treatment requires dependency on a machine, a procedure, and to a group of professional personnel. The very independent patient may therefore have difficulty tolerating dialysis. On the other side of personality types, the very dependent patient may derive some sort of satisfaction in such dependency making his/her rehabilitation back to work, school, or home activity more difficult. The medical-psychiatric liaison professional may aid the nephrology team early on in selection of a modality of treatment for renal failure (Levy and Wynbrandt 1975). In general, independent people do better in situations of less dependency such as renal transplantation, continuous ambulatory peritoneal dialysis, or home hemodialysis.

28.3 Psychiatric Complications and Their Treatment

28.3.1 Delirium

As defined (DSM-5 2013), delirium is a disturbance in attention and cognition usually developed over a short period of time. It is one of the most overlooked/underdiagnosed syndromes in the medically ill, especially in people with renal failure. Its many causes include that produced by medication and that by a medical condition. Dialysis patients are prone to many medical complications such as anemia, fluid overabundance, secondary hyperparathyroidism and uremia. Concerning the latter and its treatment, people with renal failure before and often during treatment are uremic. We know that it is not the overabundance of urea that causes this problem. For example, if one injects urea into an experimental animal it will not produce what we consider to be a uremic state. Rather, it is an accumulation of various toxic substances that are removed by a normal kidney that gives rise to it. Unlike the person with normal 24/7 kidney function, the dialysis patient is intermittently uremic, due to intermittent kidney-like function. Also, the process of dialysis in relatively rapidly shifting electrolytes and fluids may give rise to what is termed "disequilibrium syndrome" which is not uncommonly seen during and after dialysis runs.

28.3.2 Depressive Disorders and Suicide

Depressive and anxiety disorders are common complications of medical and surgical illnesses (Levy 1989). Most often the depressive disorders are precipitated by a loss that is real, threatened, or fantasized.

Patients with renal failure, especially those on dialysis sustain many such losses. Most never return to the outside work, household, or school activities they had prior to suffering from kidney failure (Cukor et al. 2013). The loss of a job is a major event in that it not only results in a loss of money, but it usually is associated with a loss of self esteem as well as a loss of the sense of masculinity in men and femininity in women. Further, patients on dialysis have a loss of personal freedom, a loss of independence, a loss of life expectancy, and a loss in their healthy appearance (Rosenthal et al. 2012). The medical regimen of these patients involves a loss of the freedom to choose the foods they like to eat and restraint in fluid intake (Gressel et al. 2014). There is usually a loss in appearance. Patients on dialysis usually have a change in their complexion in which they appear almost sun tanned, but not of a healthy looking brown. Because the avenue of access to the circulatory system involves the surgical creation of arterio-venous fistulas, both the scars of these procedures as well as the often snake-like bulging caused by the arterialization of the venous system compromises their appearance.

From the earliest days of dialysis, it was noted that the incidence of suicide in these patients seemed to be higher than in the general population or in other chronic medical illnesses. The earliest systematic study of this observation was conducted by Abram and his colleagues (Abram et al. 2001). They sent out questionnaires to all of the existing hemodialysis centers in the US at that time. With about half of the questionnaires returned and poor statistics as to comparisons, they, nevertheless concluded that suicide in dialysis patients was 500 times greater than in the general population. Although this study is a flawed one, in its somewhat dramatic conclusion it brought attention to the subject of suicide in these patient populations. To the best of knowledge of the authors of this chapter, there has been no valid study to date of suicide in dialysis or renal failure patients. The problem here is in the accuracy of statistics concerning suicide. To illustrate, in 1961 when the Nobel Prize novelist, Ernest Hemmingway left treatment for depression at the Mayo clinic and went home to Ketchum, Indiana and shot himself in his mouth, the coroner in that town registered his death as due to natural causes. Less dramatically, is not voluntary withdrawal from dialysis, a self-death? There is also a large gray area in people not adhering to diet and fluid restriction. These and other methods of self-destructive behavior, whether conscious or not border on methods of self-death.

Interestingly, when one looks as who does the act of suicide, one is confronted with interesting conclusions. For example, each year more New York City policemen die from suicide than in the line of duty. For the past several years more US servicemen and servicewomen die due to self-injury than in battle. Although there are no credible statistics, most would agree than more members of health professions kill themselves than the general population. The obvious reason seems to be that if the individual has a means of suicide at hand, there is a greater chance that the individual will meet his/her death by that means. This is the case of the dialysis patient. In years past when the portal of delivery of hemodialysis was the external arterio-venous shunts, many patients died by their disconnecting the arterial portion of their shunt. Now, as then, a method of suicide is going on a high potassium diet and/or not showing up for a few hemodialysis runs.

The accepted ideal treatment of the depressive disorders is by the use of antidepressant medications and psychotherapy. Unfortunately, the ideal and the practical treatment often do not meet in this group of patients. It has been observed and initially described (Reichsman and Levy 1972) that people with kidney failure are among the most resistive toward a psychological view of their lives. It is often rationalized by, “If you had my illness, you would be as sad as I am”. Nevertheless, the more insightful patient may be amenable to a talking therapy. Cukor and his

associates have done some groundbreaking studies on modified cognitive behavioral therapy (CBT) on dialysis patients (Cukor et al. 2013). They have shown that this form of therapy reduces depressive affect, improves quality of life, and promotes treatment adherence well within statistical significance. Medication, namely antidepressants are usually more acceptable than talk because they adhere to the traditional medical model of illness and are viewed by many as less spooky than talking therapy. A discussion of their use appears later in this chapter.

28.3.3 The Anxiety Disorders

Where there is depression there is often anxiety as well (Cukor et al. 2007). But it may also exist by itself because anxiety is the body's protective mechanism against threats to its integrity, again real, threatened, and/or fantasized. The patient treated for renal failure has many potential reasons to be anxious. For the person who has been transplanted, there is the continual fear of organ rejection. Dialysis invokes many potential fears. Since the procedure involves continual removal of blood into an apparatus and then its return, there is always the possibility of blood loss. As previously mentioned the relatively rapid removal of electrolytes and fluid often produces a transient disequilibrium syndrome, making the patient borderline delirious and possibly anxious. In center hemodialysis units it is not uncommon to see major medical problems among fellow patients including cardiac emergencies and occasionally death of patient being dialyzed. In addition, changes in staffing and waiting for medical procedures usually are associated with anxiety. Quality of life is materially affected by anxiety (De Sousa 2008).

28.3.4 The Noncompliant and Aggressive Patient

When consultation-liaison psychiatrists or other behavioral professionals are asked to speak to a group of nephrology professionals, more often than not, the subject will be "the noncompliant patient". That observation underscores the commonality of this problem for nephrology staff. As to its definition, "noncompliance" is a subjective conclusion and may vary from one observer to another. It is being used in this chapter not to include the patient who is just annoying, questioning staff, or requesting second opinions, but rather to include the very distressing, extremely demanding person including people who continually does not adhere to their medical regimen to the extreme degree.

Two factors need to be considered in studying this subject. First, renal failure patients do not represent the crosssection of society. They are heavily weighted in the direction of lower class, impoverished people, those who did not adhere to their medical regimen as hypertensives and diabetics, and people with addictive disorders. The antisocial person is overrepresented in this group of patients. Therefore, one can see why these patients, as a group may be different from the general population or other people with chronic medical illnesses in adherence to diet and other aspects of the medical regiment of renal failure. The second factor is understanding how different personality types adjust or fail to adjust to chronic medical illness. As previously mentioned the very independent or very dependent patient will respond differently to different forms of renal failure therapy. Once again, we wish to underscore the importance of the behaviorally trained professional to be involved in advising nephrology staff as the selection of a modality of treatment that compliments the personality type of the individual. Again, the very independent person should be steered in the direction of self-care or transplantation. Factors that may be helpful in the treatment of noncompliant persons include an understanding that failure to adhere to the medical regimens will result in possible hospitalizations and, more likely, a decrease in life expectancy. When noncompliance involves missing dialysis runs or aggressive behavior, it is important for staff to maintain minimal tolerance for it. Again, early on, it is important for the unit to make it clear any behavior that affects the safety of staff and patients will be treated as a police matter. Further, chronic offenders including

people who repeatedly miss dialysis runs should be transferred to other units if feasible.

Case Vignette
A 64-year-old man had been on maintenance dialysis 3 times weekly and an outpatient dialysis facility for 4 years. One day he did not show up for dialysis. He was phoned at the boarding home where he lived, and he stated he was not coming in for dialysis anymore. He gave no further explanation. The unit social worker asked the psychiatric consultant to join her for a home visit to evaluate the patient. The patient gradually revealed that he was hurt and angry because the staff nurses had been giving him relatively little attention lately in contrast to that given a new patient. He stated that he believed the nurses did not want him coming in anymore. He was reassured that he was an important member of the dialysis community. This staff nurses, who had been completely unaware of the patient's feelings, were happy to provide increased attention and socialization with the patient. For this patient the main source of social stimulation was in the dialysis unit which had essentially become a surrogate family for him.

28.3.5 Sexual Dysfunction

Many years ago Belding Scribner, an early pioneer in treating chronic renal failure observed that one-third of men on dialysis were totally impotent, one-third are partially impotent, and one-third have no impotence problem (Levy et al. 1974). This led to a few studies, most of which were conducted by questionnaires that showed that Scribner was almost correct. When women were asked about their sexual functions, a significant group, but less than men, said that they had issues of sexual dysfunction, in particular, a decrease in libido and decrease in orgasm. Renal transplant patients also have similar problems with sexual function, but at a far lesser degree than dialysis patients (Levy 1973).

There are several modalities of treatment of sexual problems in these patients. Since depression is often closely associated with sexual dysfunction, the relief of depression can reduce and even cure sexual problems in a significant group of these patients. Masters and Johnson techniques (Masters and Johnson 1970) have been used with success on selected patients. In men, the use of agents that increase the release of nitric oxide in the corpus cavernosum of the penis such as sildenafil (Viagra) and similar medications have been received as a gift to many patients.

28.4 Pharmacology of Renal Failure

In addition to its discussion in this part of this chapter, pharmacology will also be discussed later on.

Pharmacokinetics refers to the factors affecting the passage of pharmaceuticals from their entry into the body to their excretion (Callaghan et al. 1999). The five phases of pharmacokinetics are given below in bold print. *Drug absorption* is crucial because it encompasses how much of the medication actually enters the body, usually via the gastro-intestinal system. Except in rare cases of gastroparesis or GI edema, both of which are associated with slower absorption, patients with renal failure do not have any significant change compared to those with normal kidney function. *Drug distribution* refers to the concentration of that medication in body tissues. The distribution will be increased in the cachectic patient and decreased in the edematous. *Protein binding* refers to the ability of the body to bind the drug to body protein, in particular albumin. The free, unbound portion of the drug is that which is therapeutically active. Renal failure patients have a significantly diminished ability to bind pharmaceuticals to body protein, thereby making more of the drug available for both therapy and toxicity. Since virtually all medications with the exception of lithium that are used by psychiatrist have a high degree of protein binding, the general rule is that one should not prescribe for renal failure patients more than three-fifths of the maximum dose given to those with normal kidney function.

Since, the major organ for *drug metabolism,* is the liver (again, with the exception of lithium), which eliminates metabolites in bile, making drug *excretion* an issue only in those few drugs such as lithium that are excreted by the kidney in urine.

With few exceptions, most psychologically active medications are fat soluble, pass the blood-brain barrier, are metabolized by the liver, and excreted by the bowel. One should use a lower than maximum dose of every drug used in renal failure patients than those with normal renal function. This axiom should be kept in mind in the description of medications mentioned below.

When used judicially, antidepressants may be an important part of the treatment of these patients. One must keep in mind that the major handicap in the use of tricyclic medications is the potential issue of overdose in a population with a high incidence of suicide. Because of the issue of suicide and because tricyclic antidepressants are very anticholergic, the SSRI's are preferred.

Although there is less data on the use of antipsychotics in these patients, they may be used with caution. One should keep in mind the issue of QT prolongation as one would in patients with normal renal function. There is a host of potential side effects of clozapine including the more recent interest in relatively high incidence of pericarditis in those receiving this medication. The data released in the CATIE studies (Lieberman et al. 2005) indicate some advantage in the use of the older typical antipsychotics because they have a longer track record than the atypicals.

Benzodiaazepines are commonly used for the short-term treatment of anxiety, but risks may exceed benefits if used daily over the long term (see Chap. 20). Lorazepam, which is removed by the kidney in those with normal renal function, reverts to hepatic metabolism with excretion in bile in kidney failure, and therefore may be used in these patients (Lam et al., 1997).

Among the mood stabilizers, lithium is a unique medicine, especially in its use in patients with renal failure. It is dialyzable and thereby removed entirely by the artificial kidney. It may be given as a single dose after each dialysis run and will be maintained at about the same concentration in the body because its avenue of excretion, the kidney is blocked in renal failure. When the patient is dialyzed lithium's small molecule passes through the semipermeable membrane and is eliminated. There is less data concerning the use of the antiseizure medicines, chief of which is valproate. However, experience has shown that they may be used in patients with renal failure (Levy 2000).

28.5 Withdrawal from Dialysis

Consulting psychiatrists may be asked to provide perspective and advice to nephrologists when their patients wish to forego or to discontinue dialysis, particularly in cases in which the treating physician is not comfortable with a patient's decision. The willful rejection of life-prolonging treatment is an emotionally laden issue, and cognitive dissonance between patient and physician may manifest itself in assertions of patient psychopathology or in questions about the patient's capacity to make this decision in an informed manner.

It is important in such consultations to understand that they occur at a time of cultural change in the dialysis community. At its emergence in the 1960s, dialysis was a self-limiting, scarce resource. This has changed, and with availability of dialysis no longer limiting its employment, patients and caregivers have since been forced to confront the limitations and the individual, social, and ethical consequences of the treatment itself (Russ and Kaufman 2012; Russ et al. 2007). A struggle to set informed standards for the initiation and maintenance of dialysis has ensued and is reflected in the nephrology and broader medical literature of recent years. This struggle has occurred in the context of larger social dialogues centering on patient autonomy, emerging models of collaborative medical decision-making, and death with dignity.

The survival curve for ESRD (Chronic Kidney Disease Stage 5) patients on chronic dialysis is not encouraging, particularly for those with substantial comorbidities (Cohen et al. 2006; Schell et al. 2013). According to the USRDS 2009

Annual Data Report, adjusted rates of all-cause mortality are 6.3–8.2 times greater for dialysis patients than for the general population (USRDS 2010). Older age, peripheral vascular disease, major neurocognitive disorder, low albumin, and treating nephrologists' subjective impressions of survivability are significant variables in near-term mortality. The latter is according to a validated model for predicting 6-month mortality among hemodialysis patients developed by Cohen et al. (2010). The rate of dialysis withdrawal is higher among the elderly, older, and presumably more fragile patients. These patients have been a rapidly growing segment of the dialysis population. This includes the very elderly (80 years and above), whose rate of dialysis initiation increased by 57 % between 1996 and 2003, and whose subsequent 1-year mortality was a sobering 46 % (Kurella et al. 2007; Swidler 2013). Russ and Kaufman (2012) noted that the initiation of dialysis was often a matter of passive acquiescence to physician advice on the part of older patients, commenting that "older patients generally accept dialysis treatment but do not choose it." This, of course, is none too solid a footing for treatment with uncertain long-term benefits. It is in this context that the American Society of Nephrology places explicit emphasis on a shared decision-making process between patients, families and physicians in initiating dialysis (RPA; Williams et al. 2012).

For those initiating treatment, dialysis even under the best of circumstances exacts its own considerable price, and at least a fifth of patients do ultimately withdraw. Existing data point to a steady increase in this proportion, with withdrawal rate varying by age, sex, and race/ethnicity (Renal Physicians Association and American Society of Nephrology 2010; Cohen et al. 1997; Kurella et al. 2010). The stage of illness at which any particular patient reaches a threshold for discontinuing dialysis is highly individual, and is further influenced by culture, religion, and family.

Unfortunately, despite an increased awareness in the field of the limitations of dialysis in time and tolerability, and of the need for anticipatory discussions of treatment goals and end points, only a minority of ESRD patients complete advanced directives. This potentially leaves physicians and surrogates with little concrete guidance if substituted withdrawal decisions must be made (Kurella et al. 2010).

In early studies on ESRD, voluntary cessation of dialysis was indiscriminately labeled as being a type of suicide (Abram et al. 2001). While ESRD patients do in fact have an increased risk of suicide compared to the general population, withdrawal from dialysis before death occurs much more commonly, and a distinction in the psychiatric literature between pathologically-driven suicide and rational treatment termination in dialysis patients has since been recognized (Kurella et al. 2005). Rational motives for a patient to refuse dialysis are legion. If they are not transplant candidates, chronic dialysis patients suffer significant discomfort, inconvenience, and progressive functional disability, in return for which they may sometimes expect a limited extension of life on the edge of uremia. The duration of such extended life is particularly small in older and sicker patients (Chandna et al. 2011) for whom standard palliative measures offer incomplete relief of physical symptoms while adding their own side effects to the overall burden of care. Loss of autonomy and quality of life for the poor prognosis patient can reduce the effect of chronic dialysis to a prolongation of the dying process (Brown 2012). Under such circumstances, withdrawal from dialysis is appropriate and permits the facilitation of a "good death," with comfort, dignity, and brevity (Cohen et al. 2005b).

Patients may also refuse dialysis for reasons that are pathological. As elsewhere described there is an impressive array of psychiatric disorders found in the chronic dialysis/ESRD population including, most commonly, depressive and anxiety spectrum disorders, followed by delirium and major neurocognitive disorder; psychotic and substance abuse disorders are also well-represented (Kimmel et al. 1993, 2007; Halen et al. 2012; Cukor et al. 2007). Kurella et al. (2005), drawing on data from the United States Renal Data System (RDS) and the Centers for Disease Control and Prevention, have described a higher rate of reported deaths by suicide among ESRD patients as compared with the general

population. Independent predictors include advanced age, male gender, white or Asian race, geographic region, substance dependence, and recent admission for mental illness. Risk for suicide was found to be highest in the first 3 months after initiation of dialysis, subsiding thereafter. Dialysis-dependent patients can also more passively take their own lives by missing treatments and medications, engaging in dietary indiscretions, and ignoring fluid restrictions. Rosenthal et al. (2012) found depressive affect as measured by the Beck Depression Inventory to be a significant predictor of mortality in a cohort of 130 urban ESRD patients on hemodialysis, with a concurrent, strong association noted between depression and medication nonadherence. Consulting psychiatrists are commonly asked to help distinguish pathological from benign motives in patients refusing dialysis and to guide physicians struggling with the decision of whether to honor or challenge these refusals. In such a consultation, the most important initial decision made by the psychiatrist is how stringent a test to apply for capacity.

The setting of a situation-specific standard for capacity by the consultant is substantially influenced by the perceived risks and benefits of the proposed dialysis and by whether a refusal can be considered medically reasonable under the circumstances. The consulting psychiatrist should discuss these case-specific issues with the treating nephrologist and should be aware that the Renal Physicians Association (RPA) deems it appropriate to withhold or withdraw dialysis under a number of circumstances. These include the direct request of acute renal failure or ESRD patients with decision-making capacity; incapacitated patients who have previously refused dialysis in oral or written directives, or whose legal agents refuse dialysis in their behalf, patients with irreversible, profound neurological impairment lacking evidence of awareness, thought, sensation, and purposeful behavior (RPA 2010; Cohen et al. 1997, 2003; Moss 2001). In addition, the RPA recommends consideration of forgoing dialysis for patients with a very poor prognosis or for whom administration of dialysis is unsafe—including patients with advanced major neurocognitive disorder who are unable to cooperate with the procedure itself (RPA 2010). One potential pitfall in the nephrology recommendations should be noted. From the consulting psychiatrist's point of view, it is troublesome to uniformly assign a low capacity standard for dialysis refusal to those patients who are uncooperative or combative with the dialysis procedure, as they may include individuals with psychotic, neurodevelopmental, or mood disorders that are potentially treatable. Likewise, the consulting psychiatrist must tread carefully around the determination of irreversibility of neurological impairment, being aware that it is not unknown for renal failure to precipitate catatonia (Huang and Huang 2010; Carroll et al. 1994).

In setting capacity standards, it is also helpful to refer to the degree to which patients' decisions are culturally endorsed and supported by family and loved ones. This is not to say that an individual patient's decision must be popular. Rather, it is to say that to the degree a decision to terminate dialysis conflicts with a patient's traditional values and imperils social bonds, suspicion of a capacity-altering mental illness should be heightened. In such cases, a more exacting examination of the patient's information-processing and reasoning is appropriate.

In addition to setting an appropriate threshold for decision-making capacity, it is important to be cognizant of the fact that psychiatric illness in and of itself cannot be equated with incapacity to refuse dialysis.

The existential, spiritual or developmental struggles at the end of life should not be unnecessarily labeled as pathological. Ambivalence and even anguish about relinquishing life-prolonging treatment is to be expected, and may also be found in those parties most intimately involved in the patient's life and care. Nonetheless, severe psychiatric disorders can be incapacitating and should be ruled out in cases of life-threatening noncompliance and early dialysis termination. Major depressive disorder, particularly when complicated by psychosis can readily interfere with an individual's ability to retain, weigh, and cognitively process information and should be suspected in clinically suspect dialysis refusals (Cohen et al. 2003). There are instances in which

it is appropriate and necessary to defer dialysis discontinuation while treating comorbid psychiatric illnesses (Cohen et al. 2003).

As previously noted, the concept of "shared decision-making" is now emphasized in dialysis decisions (RPA 2010; Williams et al. 2012). Often the need for a capacity determination is itself an indication of failure in a shared process that should ideally build consensus among stakeholders, including patient, family, physicians, and other significant caregivers (Cohen et al. 2003). A number of potential sources of conflict are described in the RPA recommendations, including miscommunication or misunderstanding about the patient's prognosis, participant values, interpersonal, and individual issues. From the psychiatric perspective, reframing a capacity consultation to focus on restoring dialogue between participants may be a more helpful intervention than seemingly vindicating one or another party. Where a consensus cannot immediately be reached, RPA guidelines suggest considering a time-limited dialysis. In the event of emergent circumstances, the RPA recommendations suggest providing dialysis with the consent of the patient or legal designate while allowing conflict resolution to proceed. The psychiatric consultant may be called upon to provide an emergent, temporizing capacity determination if such consent is withheld. It should be reiterated, however, that while shared decision-making and stakeholder consensus is the ideal, patients with intact decision-making capacity have the right to unilaterally refuse dialysis.

Once a decision has been made to withhold or terminate dialysis, it can be anticipated that lethargy, coma, and death will ensue within a mean time of 8 days. The International Dialysis Outcomes and Practice Patterns (DOPPS) study found that 79.1 % of patients died within 10 days of withdrawal (Cohen et al. 2006; Fissell et al. 2005). It has been traditionally taught that uremic deaths are gentle. However, retrospective, family-derived data have described severe pain in a preponderance of dying ESRD patients during the last week of life (Cohen et al. 2005a). This highlights the fact that psychiatric consultation does not necessarily end with the withdrawal of dialysis. The termination of life-prolonging treatment provides an opportunity for the psychiatric consultant to help smooth the transition of the patient's care to a primary goal of palliation.

28.6 Palliative Care

Patients with ESRD are defined by clinical suitability for dialysis or transplantation. These patients are an at-risk population for vascular events, with increased risks of acute myocardial infarction, congestive heart failure, and cerebrovascular accidents/transient ischemia and with accompanying graded increases in mortality from these conditions with advancing kidney disease (United States Renal Data System 2012). These patients are increasingly elderly with multiple comorbidities, entering ESRD with a median age of 65 (Cohen et al. 2006) and with a mortality rate eight times that of the general Medicare population (Werb 2011).

Prognosis in ESRD is felt by the Renal Physicians Association (2010) to be particularly poor for patients with at least two of the following: age 75 years or greater, high comorbidity, marked functional impairment, and severe, chronic malnutrition. The RPA (2010) now recommends prognostic estimates be provided to patients with Acute Kidney Injury, Stage 5 Chronic Kidney Disease (ESRD). Proximal causes of death in patients with renal failure are for the most part related to cardiovascular events, but septicemia, dialysis withdrawal, stroke, sequelae of calciphylaxis, and complications of diabetes are also represented in ESRD deaths (Werb 2011).

In addition, psychiatric syndromes, anemia, and diseases of bone, skin, and joints are frequently found. To this substantial burden of illness is added the systemic and growing effect of uremia itself, along with symptoms referable to treatment. Chronic pain in hemodialysis and ESRD patients is common, significant, and often ineffectively managed (Davison 2003, 2005).

Taking mortality and illness burden into account, dialysis patients are often appropriate for consideration of palliative care (Werb 2011; Davison 2003, 2005). Unfortunately, ESRD care

in the United States tends to be fragmented and poorly reflective of patient goals and prognosis, with uneven and inadequate access to palliative care resources (Kurella and Meier 2013).

28.6.1 General Issues in Renal Palliative Care

End Stage Renal Disease patients live with protracted somatic discomfort. As a group, patients have been described as suffering an average of 10.5 symptoms at any given time, including most prominently fatigue, pruritis, pain, cramps, sleep disruption, anorexia, and constipation (Merkus et al. 1999; Valderrqabano et al. 2001; Weisbord et al. 2003). Sexual dysfunction is also common and is discussed elsewhere in this chapter. Remedies are available for most symptoms, but are limited in efficacy and tolerability. Issues of comfort and palliation have a direct impact on the course of intercurrent psychiatric conditions. Consulting psychiatrists should be aware of some common issues in renal palliative care and should tailor interventions to add to patient comfort during life-prolonging treatment as well as during the dying process.

Fatigue is common and multifactorial in etiology. Sleep disturbance, anemia, physical deconditioning, and depression may contribute, in addition to hyperparathyroidism, uremia, and effects of dialysis itself (Murtagh and Weisbord 2010). Exercise, cognitive interventions, and other nonpharmacological measures should be integrated into treatment where possible (Murtagh and Weisbord 2010). Other nonpsychiatric issues such as hypothyroidism should be ruled out, and treatment of kidney disease-related anemia with erythropoietin-stimulating agents considered (Murtagh and Weisbord 2010). Existing psychotropic medications should be reviewed in order to minimize those with potential for contributing to sedation, anergia, and abulia. A psychostimulant like methylphenidate may be used symptomatically (Cohen et al. 2006).

Pain is reported by 50–63 % of dialysis patients (Cohen et al. 2006; Merkus et al. 1999), and may be even more prevalent among those who are dying (Cohen et al. 2005a). Pain may be acute or chronic, nociceptive, somatoform, visceral, neuropathic, or complex regional in distribution. Like sleep disturbance, pain in ESRD patients may have multiple potential etiologies, including the primary renal disease itself, comorbid conditions, downstream complications, or dialysis treatment (Davison et al. 2010). The Renal Physicians Association refers practitioners to an evidence-based tool for pain management in dialysis patients developed by the Mid-Atlantic Renal Coalition (MARC) and the Kidney End-of Life Coalition (2009). The Clinical Algorithm & Preferred Medications to Treat Pain in Dialysis Patients (http://www.kidneyeol.org/painbrochure9.09.pdf) provides specific recommendations on the use of non-opioid and opioid agents in CKD/dialysis patients, with opioids employed at moderate to severe pain levels. In considering these recommendations and the comments below, it should be borne in mind by the consulting psychiatrist that the use of narcotic analgesics in chronic, nonmalignant pain remains clinically controversial and potentially problematic. The employment of opioids is most clearly appropriate in the palliative management of patients suffering from pain due to end stage, time limited disease. Analgesic therapy in ESRD relies on the "analgesic ladder" developed by the World Health Organization. It proceeds sequentially from nonopioid with or without adjuvant therapy to weak opioid and ultimately to strong opioid levels of analgesia, maximizing each level in turn before moving to the next, with nonopioids and adjuvants accessible at all levels (Davison et al. 2010). Opioid dosages are individualized by effect and tolerability, rather than by standard dosing. Weak opioids can have dose limitations due to compound formulation with nonopioid agents like acetaminophen or by disproportionate adverse side effects at high doses (Davison et al. 2010). The use of opioids requires an active collaboration between physician and patient, including patient education and consent, reassessment of target pain symptoms, assessment, and description of observed symptomatic and functional benefits. One should monitor and manage opioid-related side effects, with appropriate

documentation. There is extensive literature to guide the physician in the choice and dosing of particular opioid agents in context of renal failure (Davison et al. 2010). Morphine is avoided in this population due to accumulation of its neurotoxic 6-glucuronide metabolite, which can lead to prolonged coma and myoclonus (Werb 2011). Meperidine cannot be recommended, given its neurotoxic metabolite normeperidine, with its potential for precipitating agitation, delirium, psychosis, and seizures, and its accumulation in renal impairment (Davison et al. 2010). Methadone may also bear watching from the standpoint of the consulting psychiatrist, given its potential for QTc prolongation and attendant risk of Torsade de Pointes (Krantz et al. 2002; Sekine et al. 2007). Davison et al. (2010) consider hydromorphone and fentanyl to be better alternatives among the strong opioid medications. It should be noted that psychotomimetic potential has been noted with mixed agonist-antagonist analgesics (butorphanol, nalbuphine, pentazocine) and that *N*-methyl-D-asparate (NMDA) antagonists might in theory be effective in hyperalgesia or loss of opioid effect (Inturrisi 2002). Adjuvant psychotropics are often added for management of neuropathic pain, especially tricyclics like amitriptyline and anticonvulsants like gabapentin. Although enterically metabolized, the usual caveats apply about the use of tricyclics in elderly patients and in those vulnerable to delirium, constipation, and seizure. The common comorbidity of renal failure and cardiac disease is also something to consider when prescribing tricyclics as adjuvants in dialysis patients, as well as the potential for a lethal outcome of overdose in this at-risk population. It should be noted that among tricyclics, desipramine is 70 % renally excreted; the drug and its 2-hydroxy metabolite can accumulate in renal failure and are not removed by dialysis. About half of protriptyline's elimination is by a slow renal excretion; it is also nondialyzable. Gabapentin is commonly prescribed in neuropathies. It is excreted unchanged in the urine; dosage must be adjusted downward for creatinine clearance and supplemental posthemodialysis doses must be given. Blood levels of carbamazepine and valproic acid need to be monitored. Carbamazepine is substantially dependent on renal excretion. Despite limited dependence of the drug on renal elimination, free valproic acid levels can be elevated in renal failure. Among the SNRI antidepressants, duloxetine has come into play as a treatment for pain related to diabetic neuropathy, along with fibromyalgia and chronic musculoskeletal pain. However, it is dependent on renal elimination and is contraindicated in renal failure.

Sleep disruption is common among ESRD patients, with a prevalence far higher than among the general population, ranging from 20 to 83 % in studies of dialysis patients (Murtagh and Weisbord 2010) and a high incidence of formal sleep disorders, including restless legs syndrome, periodic leg movements disorder, and sleep apnea has been documented (Cohen et al. 2006; Kimmel et al. 1997). Obstructive sleep apnea may be particularly prevalent among ESRD and dialysis patients, with resultant psychiatric and systemic comorbidities (Murtagh and Weisbord 2010) Iliescu et al. (2003) have documented a relationship between poor sleep quality as measured by the Pittsburgh Sleep Quality Index and depression among hemodialysis patients. Other than the standard methods of sleep hygiene and treatment of primary sleep disorders, the efficacy of symptomatic treatments for insomnia in uremic patients is not clear (Pieta et al. 1998). There is also additional risk in uremic patients of precipitating neuropsychiatric side effects with medications (Pieta et al. 1998; Sloand et al. 2004). Short-term treatment of insomnia with sedative hypnotics can be considered if sleep apnea is not present. These may include low to standard doses of zolpidem, temazepam, flurazepam and trazodone. In dialysis patients, particularly those with cardiac disease, it is worth noting that trazodone may contribute to hypotension and that trazodone-associated arrhythmias have been reported (James and Mendelson 2004). Triazolam at low doses is also considered a renal hypnotic. Its potential for inducing rebound insomnia, anterograde amnesia, and behavioral disinhibition is likely no greater than that of other benzodiazepines (Rothschild 1992; Mendelson and Jain 1995). However, potential for contributing to delirium is significant.

Anorexia is found in 25–48 % of chronic dialysis patients (Merkus et al. 1999), and is potentially multifactorial in its etiology. Reversible, nonpsychiatric causes should be investigated and treated and nutritional support provided; adequacy of dialysis should be ensured (Murtagh and Weisbord 2010). Medications contributing to dry mouth and constipation, particularly those with anticholinergic properties should be reduced or eliminated if possible. Metoclopramide has been suggested (Murtagh and Weisbord 2010), but from the psychiatric perspective extrapyramidal side effects, abulia and depression would be concerns. Depressive disorders should be investigated in malnourished patients (Cohen et al. 2006) and treated if present. In the treatment of depressive disorders accompanied by anorexia, side effect profiles of psychotropic agents like mirtazapine can be used to advantage, if bowel motility and sensitivity to sedation allow.

28.6.2 Psychiatric Aspects of Renal Palliative Care

Palliative care should be initiated well in advance of actual dialysis withdrawal, and should be anticipatory in its approach to management (Davison et al. 2008). Psychiatric treatment is an essential aspect of this management both before and during hospice, and should attend to ongoing emotional needs as well as discrete end-of-life symptoms such as agitation. Psychotherapeutic interventions in the hospice setting are generally supportive, directed at helping the patient and loved ones make the best use of the remaining time before the advent of terminal uremia and loss of awareness. Life review, expressions of love and devotion, and the specific addressing of "unfinished business" between patient and family may all have necessary roles in the leave-taking process. As the patient's window of lucidity closes, the clinician at bedside will often direct increased attention to the bereaved survivors.

Patients will come to palliation with their own clinical histories and ongoing psychiatric issues. Psychiatric treatment begun in prepalliative phases of renal failure is dealt with elsewhere in this chapter. Among the decisions that need to be made as the patient's level of awareness declines and end of life approaches is at what point to taper maintenance psychotropic agents, including antidepressants and mood stabilizers. This will be a risk/benefit decision based on multiple factors including the perceived ongoing clinical benefit of maintenance agents, any history of rapid deterioration of them, evidence of their accumulation, and toxicity. Eventually, it can be expected that supervening lethargy will lead to a progressive streamlining of the patient's regimen.

In contrast to psychopharmacology begun in the advanced but stabilized renal failure patient, psychiatric pharmacotherapy initiated in the final week of life is shorter term and symptom-driven rather than syndrome-driven, targeting changes in mental status potentially disruptive to the comfort and dignity of the patient. When terminal delirium is accompanied by agitation, haloperidol is the mainstay psychotropic (Neely and Roxe 2000), as it is hepatically metabolized, and has inactive metabolites. It may be used at 0.5–1 mg po/SQ/IM/IV hourly, titrating to effect (Neely and Roxe 2000). Akathisia, dystonia and Parkinsonism can be dealt with by using diphenhydramine 25–50 mg IV q 4–6 h in the usual manner (Neely and Roxe 2000), although the use of this agent will likely hasten cognitive decline. Haloperidol and benzodiazepines can be employed in the short period of postdialysis palliation to quell intercurrent anxiety, affective lability, and sleep disturbance. As always, the consulting psychiatrist should be alert for paradoxical disinhibition and accelerated confusion when using benzodiazepines in the neuropsychiatrically compromised patient.

It should be noted that the postdialysis dying process involves role transition for the caregivers, as well as for the patient and loved ones. Doctors, nurses, and ancillary staff may be susceptible to feelings of helplessness and professional inadequacy in context of death, particularly if the relationship with the patient has deepened over time. Psychiatric consultation during this critical period also includes maintaining an awareness of distress experienced by members of the renal team and responding supportively to it.

28.7 Renal Transplantation

The selection process for potentially eligible patients and living donors includes psychosocial assessment, often employing instruments capable of highlighting those candidates meriting more complete examination by a transplant team psychiatrist (DeMartini et al. 2005). There are at least a couple of general transplant screening instruments available, including the Psychosocial Assessment of Candidates for Transplantation (PACT) and the Transplant Evaluation Rating Scale (TERS) (DeMartini et al. 2005; Olbrisch et al. 1989; Twillman et al. 1993).

The psychiatric consultant assesses potential donors and recipients with regard to their psychiatric histories, coping styles, available systems of support, motivations for candidacy, and decisional capacity (Cohen et al. 2006). The psychiatrist is asked to assure the team that candidates and donors are capable of informed consent to renal transplant and that organ donation itself is altruistic and not coerced. The consulting psychiatrist is also expected to identify behavioral "red flags" likely to impact on patient survival. When psychiatric problems affecting candidacy are identified, the consultant may be called upon to help the candidate stabilize sufficiently to become eligible.

Capacity may be affected by misunderstanding of the procedure and its probable results. Unrealistic expectations of return to a predisease state of health should be uncovered in the course of assessment, as should significant gaps in the patient's understanding of the posttransplant burden of care and the risks of noncompliance. Cognitive impairment from delirium or uremic dementia should be detected and its effect on the patient's decision-making capacity determined. In this respect, a pretransplant capacity evaluation should include a structured cognitive assessment tool, with or without formal neuropsychological testing. As an example, the Structured Interview for Renal Transplantation (SIRT) has been developed by Mori and colleagues as a comprehensive tool and clinical guideline for the pretransplant assessment of the renal patient. It collects information relevant to the transplant team's assessment and decision, including data on the patient's understanding of the illness, coping style, mental health history, and cognition (Mori et al. 2000).

It should be recognized that the presence of a psychiatric history itself does not preclude a patient from giving valid, informed consent to renal transplantation, particularly if the psychiatric illness has been responsive to treatment (Cohen et al. 2006). Even patients with prohibitive burdens of psychopathology, including psychosis and suicidality, can be treated and reevaluated for capacity when in remission.

Aside from the question of capacity, limited available data do not indicate that psychiatric disorders should be considered automatic contraindications to renal transplantation, particularly in the setting of good social supports (Carrasco et al. 2009). Pretransplant patients can suffer progressively increasing anxiety and depression while awaiting an organ (Corruble et al. 2010), while there is at least some data indicating that prevalence of anxiety and depression may diminish after transplantation (Lopes et al. 2011; Szeifert et al. 2010).

Available data do show renal transplant candidates to be less candid than the general C/L population about past psychiatric treatment history (Mori et al. 2000; Rundell and Hall 1997). This is problematic since survival of transplanted organ recipients is dependent on strict treatment compliance, which can be undercut by psychiatric disorders, including anxiety disorders, depressive disorders, and substance use disorders (DeMartini et al. 2005). In one longitudinal study, depression and age were the two most important predictors of survival in renal candidates (Mori et al. 2000; Levenson and Olbrisch 1993). Levy (1994) identifies as higher risk those patients who have become psychiatrically symptomatic in context of ESRD and dialysis. He also points out family history of psychiatric illness as a significant factor, and stresses the necessity of pretransplant education about the possible complications of immunosuppressant therapies as a buffer against unpleasant surprises (Levy 1994). Active substance abuse contraindicates transplantation, though patients with at least 6 months' abstinence can be reconsidered (Cohen et al. 2006),

particularly if active in treatment. Personality disorders are likely to pose a challenge to the patient's ability to work with the treatment team and to the team's ability to metabolize the patient's behavior. Personality-disordered patients are, when transplanted, likely to require a specialized behavioral treatment plan with close coordination among psychiatric and non-psychiatric team members. The consultant's pretransplant role with these patients includes helping the team to realistically gauge whether its program will be able to effectively contain the patient. As always, past history of treatment compliance is the most direct predictor of a candidate's future behavior. A pattern of missed dialysis sessions, dietary indiscretions, and medication noncompliance contraindicates renal transplantation (Cohen et al. 2006).

The capacity of candidate donors is subject to its own set of potential failings. Given that the procedure offers under the best of circumstances no benefit to the health of the donor, a high standard of capacity should be required in terms of retaining and understanding risks and potential consequences. Leo et al. (2003) identify chronic psychosis, severe affective disorders, suicidality, intellectual developmental disorder, unremitted substance use disorder, and severe personality disorder as conditions likely to preclude well-informed decisions about renal donation.

The consultant also needs to assess the individual donor's motivation. Inappropriate familial pressure or unfair external emotional leverage on a candidate donor may preclude exercise of a valid choice. Guilt, fear of retaliation, and expectations of reciprocal emotional commitment are additional examples of inappropriate donor motivations. Unexplored ambivalence may ultimately sabotage donor compliance with preoperative protocol (Leo et al. 2003), and Levy (1994) feels that "the potential donor with an ambivalent relationship with the recipient should not be encouraged to donate". Financial enticements of donors are both unethical and illegal. Leo et al. (2003) offer a useful guideline for the structured interview of prospective kidney donors. Baskin (2009) points out the ethical challenges inherent in evaluating unrelated prospective solid organ donors, and in attempting to more clearly understand motives presented as purely altruistic.

There is very limited psychiatric outcome data on donors posttransplantation. A recent modestly sized, prospective study based on a Symptom Checklist administered before and after donation indicated an overall increase in psychological symptoms over time, though not generally of clinical significance, and difficult to distinguish from fluctuations found in the general population (Timmerman et al. 2013). A retrospective review by Rowley et al. (2009) found that kidney donors with histories of psychiatric illness who underwent preoperative psychological evaluation and were cleared for donation tolerated the procedure and its aftermath without psychological deterioration. For the consulting psychiatrist this once again serves to highlight the importance of preoperative clinical screening of the prospective donor.

Postoperative psychiatric issues are not uncommon among renal transplant patients. Data from Fukunishi et al. (2001) show a peak prevalence of psychiatric disorders among adult living-related renal transplant recipients of 28 %, occurring 3 months after surgery and subsequently declining at 1 and 3 years. Delirium is the most common disorder during the early postoperative period, closely followed by major depressive disorder, persistent depressive disorder, and adjustment disorders. Brief psychotic disorder, somatic symptom disorder, substance-induced disorders, and posttraumatic stress disorder are also represented. There has been at least one documented case of hyperactive delirium followed by catatonia after liver and kidney transplantation (Kalivas and Bourgeois 2008).

Postoperative delirium in renal transplant patients can be precipitated by diverse factors, including narcotics, immunosuppressant, and glucocorticoid-induced neurotoxicity, infection, and residual uremia (Cohen et al. 2006). Patients with major neurocognitive disorders are at increased risk for delirium. As in all delirium management, identification and correction of precipitants is the primary approach, with adjunctive use of medications for symptomatic management of agitation, disorganization, disinhibited

behavior, hallucinosis, and delusions. Haloperidol, oral or parenteral, remains first-line medication for agitated delirium (Cohen et al. 2006). Atypical antipsychotics such as risperidone can be tried, although hypotension and reflex tachycardia are of concern. It should be noted that all antipsychotics commonly used in delirium carry the risk of QT interval prolongation with attendant arrhythmias.

Depression is the most common longer-term psychiatric problem afflicting renal transplant recipients, found in children and adolescent recipients as well as among adults (Ghanizadeh et al. 2009). Nowak et al. (2010) cite a prevalence rate of 22 % in an outpatient transplant center cohort. It should be recognized by the consultant and by the transplant team that in addition to attendant psychological suffering and suicide risk, depression may have a pernicious effect on posttransplant medication compliance and disease survival. Found a significant correlation between score on the Beck Depression Inventory-II and the likelihood of lapses in compliance with immunosuppressant medications in an urban kidney transplant population, with depression accounting for 18 % of variance in adherence scores. Data from a Netherlands cohort indicated that preexisting depression persisted after transplantation and that it was associated with cardiovascular and all-cause mortality (Zelle et al. 2012). In a prospective cohort study of outpatient kidney transplant recipients, Nowak et al. (2010) found that in a prospectively followed cohort of recipients depression, as measured by the Center for Epidemiologic Studies—Depression scale was significantly associated with 5-year mortality and was predictive of graft loss.

Etiologies and contributing factors to depression in transplant recipients are diverse, ranging from pharmacological to psychodynamic. Posttransplantation depression can be precipitated by immunosuppressant medications, including steroids (Levy 1994) and by graft rejection (Iwashige et al. 1990). Tsunoda and colleagues have identified social isolation (living alone) as a particularly strong demographic predictor of depression among patients following kidney transplantation (Tsunoda et al. 2010), while Zelle et al. (2012) have also identified associations of posttransplant depression with lower physical activity level, inability to work, proteinuria, and longer dialysis duration. A paradoxical depressive syndrome in the presence of successful transplantation has been described by Fukunishi et al. (2001) as occurring in 5 % of kidney recipients. They have felt it to be precipitated by guilt regarding the donor's sacrifice. A subsequent study by Sugawara et al. (2008) has identified 25 such cases among a cohort of 1,139 renal transplant recipients. They did not identify guilt as the prominent dynamic, but cited rather the mourning of an imagined past, irretrievably lost to chronic illness (Baines and Jindal 2002).

Transplanted patients are also vulnerable to anxiety caused by medications as well as by the chronic threat of rejection and organ failure. Psychological discomfort with the donated kidney can be an ongoing issue for the patient, with "internalization" of the foreign organ occurring only incrementally (Levy 1994; Muslin 1971). The psychiatric consultant should also be aware that tacrolimus itself can precipitate anxiety and akathisia—with clinical incidence related to plasma level (DeMartini et al. 1996).

Antidepressant management and anxiolysis in ESRD are discussed elsewhere in this chapter, with similar concerns for the transplant patient in the transitional postoperative period. Mania, including that produced by glucocorticoids can be treated with mood-stabilizers, with considerations attendant to renal management as elsewhere noted. Steroid-induced psychotic disorder should prompt treatment with antipsychotic medications.

It should be noted that altered pharmacokinetics in the setting of resolving renal failure continues to affect the selection and dosing of psychotropic medications in the posttransplant period. The consultant should also be aware that most maintenance psychotropic medications are held on the day of surgery. Since most of these medications are not dependent on renal metabolism, they should generally be restarted postoperatively. Medication withdrawal is of particular concern in patients maintained on

benzodiazepines, and perioperative institution of an equipotent dosage of parenteral lorazepam should be considered.

Pharmacotherapy after renal transplantation is complicated by the presence of immunosuppressants in the patient's regimen. The psychiatric consultant should be aware of the psychiatric effects of immunosuppressants commonly used in renal transplantation. As detailed by DeMartini et al. (2005), each immunosuppressant agent is associated with common, annoying side effects and with less common but more worrisome neurotoxic symptoms. Cyclosporine commonly causes headache, restlessness and tremor; a minority of patients can suffer delirium, medication-induced psychotic disorder, cortical blindness, seizures, loss of speech, and coma. Cyclosporine neurotoxicity can precipitate posterior reversible encephalopathy syndrome (PRES), can cause demyelination, may be likelier with higher doses and IV administration, and may be potentiated by hypocholesterolemia, hypertension, and hypomagnesemia (DeMartini et al. 2005; Kim et al. 2011). Tacrolimus commonly causes tremor, restlessness, insomnia, vivid dreams, hyperesthesias, and headache. It can also cause anxiety and akathisia. Neurotoxic states can manifest in agitation, dysarthria, delirium, seizures, hemiplegia, cortical blindness, posterior reversible encephalopathy syndrome (PRES), and coma. Tacrolimus neurotoxicity can be mediated by demyelination, is associated with higher plasma levels and with pathology that disrupts the blood-brain barrier (DeMartini et al. 2005; Kim et al. 2011). Demyelinating syndromes or PRES will require imaging, ideally magnetic resonance imaging (MRI), for diagnosis. Tacrolimus neurotoxicity can appear at substantial delay if blood level rises, as seen in a recently-reported case of medication-induced mania and psychosis occurring 17 years after kidney transplant (Bersani et al. 2013).

Azathioprine may precipitate depression, although reports are confounded by the presence of other possible culprit medications (DeMartini et al. 2005). Mycophenolate mofetil may also be associated with neuropsychiatric toxicities, including medication-induced anxiety, psychotic and depressive disorders, agitation, delirium, somnolence, paresthesias, hypertonia, and seizures; here again, however, concurrent administration of corticosteroids and cyclosporine clouds the issue (DeMartini et al. 2005). The panoply of steroid-induced neuropsychiatric syndromes will be familiar to the practicing consultation psychiatrist.

Calcineurin inhibitor agents like tacrolimus and cyclosporine require therapeutic blood levels to prevent rejection and are more prone to cause neurotoxicity when supratherapeutic (DeMartini et al. 2005). For this reason, particular attention needs to be paid to pharmacokinetic interactions of immunosuppressants with psychotropics, particularly those blocking or inducing the cytochrome P450 IIIA4 subsystem. As described by Manitpisitkul and colleagues (2009), CYPIIIA4 inhibitors such as nefazodone and fluvoxamine can elevate both cyclosporine and tacrolimus levels and nefazodone has been shown to increase these drugs' levels by a factor of 10. In vitro data would indicate that sertraline would be least liable to IIIA4 inhibition among the selective serotonin reuptake inhibitor (SSRI) antidepressants, though there is conflicting data on its effects on cyclosporine levels. Fluoxetine, citalopram, and paroxetine do not alter cyclosporine levels and the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine also has little IIIA4 effect. Nefazodone should certainly be avoided. Solid information on the SNRIs desvenlafaxine and duloxetine is lacking (Manitpisitkul et al. 2009). Carbamazepine can induce hepatic metabolism and precipitate a decrease in cyclosporine levels, resulting in organ rejection. In this respect, valproate may be a less problematic choice. Use of the common herbal psychotropic St. John's Wort can also induce CYP450 IIIA4 and decrease both cyclosporine and tacrolimus levels (Cohen et al. 2006). Immunosuppressant medications may affect psychotropic blood levels; an example of this would be the potential for cyclosporine to raise levels of quetiapine or for tacrolimus to precipitate hypotension with mirtazapine (Fraile et al. 2009).

Pharmacodynamic interactions of psychotropics with immunosuppressants may also occur.

An example of this would be serotonin syndrome precipitated by synergism between cyclosporine and sertraline (Wong et al. 2002). Other examples would be the potentiating of lithium nephrotoxicity by calcineurin inhibitors, combined effects of antipsychotics, and calcineurin inhibitors on QTc and mycophenolate-clozaril agranlocytosis (Manitpisitkul et al. 2009).

Finally, the consultant should be aware that there have been cases of intentional overdose of immunosuppressants by suicidal patients, along with cases of unintentional toxic ingestion. Acute overdoses of tacrolimus have been remarkably well-tolerated (Curran et al. 1996; Mrvos et al. 1997; Sein et al. 2005), although there is at least one report of inadvertent toxicity leading to self-injurious and aggressive behavior (Hardoy et al. 2012). Cyclosporine overdoses have been more injurious, with neurotoxicity the most salient acute effect (Zylber-Katz et al. 1994; Sketris et al. 1993; Nghiem 2002) and with one recorded death due to intracerebral edema in an accidental intravenous overdose (De Perrot et al. 2000). In acute tacrolimus toxicity CYP450 IIIA4-inducers like phenytoin have been used to bring down levels more quickly (Jantz et al. 2013).

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