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Common Psychiatric Problems in the Well Transplant Patient

Mark W. Nickels

The well transplant patient faces significant psychological challenges in returning to health. The challenges begin long before transplant with the struggle to cope with the fears that accompany serious threats to health and role function. Loved ones also must face these challenges. Primary care providers have a valuable role in assisting patients and their families regain health through the provision of ongoing support; by helping them appropriately express their fears, anger and anxieties; by educating them all along the way; and by setting attainable goals and praising their achievement of them. Psychiatric difficulties that arise can include cognitive difficulties; psychiatric side effects of the immunosuppressants; major depression; anxiety disorders such as panic disorder, post-traumatic stress disorder, and generalized anxiety disorder; and non-compliance. These difficulties can be addressed through a variety of interventions, including the use of psychotropic medications and referring patients to mental health professionals.

Cassell defines suffering as that which is experienced when there is actual or perceived threat of integrity of continued existence of the whole person. Hence, a significant part of suffering is apprehension.
As time passes and the transplant recipient gradually improves, patients and families begin the process of adapting to improved health and function. While it seems that this should occur easily, difficulties can arise during this period as well. Patients may be apprehensive about their abilities to function fully again and may show increased focus on minor health issues. Even those recipients who do well physically may worry about future transplant problems as they recall the difficulties endured thus far. Some recipients may experience an emotional ‘let-down’ as family members shift their attention away from them and back to the normative issues of daily life. In other instances, patients feel their families are too intrusive, hovering over them and reacting to minor problems as if they are still quite ill.

All patients and families who undergo transplant deal with these things. Some are relatively successful, while others have significant difficulties. Still, patients who undergo transplant often find an improved quality of life (QoL). As a concept, QoL is variably defined and research into it varies dramatically. In addition, many possible biases exist. For example, Rundell and Hall suggest that pretransplant patients may under-report psychiatric issues for fear of not being listed as a candidate. Regardless of definition or parameters used in the research, it seems clear that many patients show improved QoL. Colonna and colleagues found that all 28 patients studied who underwent liver transplantation reported improved QoL. Leyendecker and Lowe each reported improved QoL after liver transplantation to the level of the general population. Collis, however, reported that improvements in QoL post-liver transplantation did not reach the level of the general population. And, Tarter and Bryan noted that while QoL improves after transplantation, it may not reach the patient’s pretransplant status.

A number of factors may impact post-transplant QoL. The chronicity of the pre-transplant illness may be a factor in QoL. Data from studies of patients with chronic illnesses show that such patients can have elevated levels of anger and hostility, especially in males; females tend to experience greater levels of anxiety. And elevated levels of anger and hostility can impair social connectedness and supports. Leiker found that higher levels of hostility were associated with poor health habits including neglect of exercise, poor nutrition, and the use of alcohol and drugs. In addition to the mere presence of anger and hostility, the expression of these also plays a role. If the expression of anger and frustration is inhibited, patients can experience greater distress and depression, have worse perceived health and greater interference with life activities, and greater pain intensity and pain behaviors. Pain intensity is often subjectively rated by those experiencing the pain through the use of a scale. Quality of Life is often researched using subjective rating scales. These scales may include measures of:

- physical health
- activity level
- social/family function
- hope/optimism
- psychological health
- socioeconomic status, etc.

If expressions of anger and frustration are under-controlled, such as in tantrums or rages, increased interpersonal conflicts and poor compliance can follow. Fernandez suggests that other emotions—fear and sadness—are key factors in the experience of distress in patients with chronic pain. Hence, pre-morbid psychiatric difficulties, illness chronicity, patient coping styles and their personality traits may all have an impact on the adequacy of post-transplant adaptation.

Post-transplantation factors play a role. Physical difficulties, including fatigue, impotence and medication side effects can adversely impact QoL. Kober notes the number of rejection episodes is inversely associated with QoL. And, improvement in encephalopathy, especially in subtle cases, contributes significantly to enhanced QoL.

Post-transplant self-perception is important in QoL. Stilley and colleagues report a robust association between health concerns and recipient psychological status. Patients who perceive themselves as being more active and psychologically functional show better levels of energy, function, work function and social activity. Factors linked with improved self-perception include reduced burden of physical distress, lesser reliance on permanent disability benefits, high levels of mastery and self-esteem, increased levels of self-efficacy, and social influences toward healthy functioning and health-related lifestyles.

Finally, the level of social support and the presence of pre-morbid personality difficulties may impact QoL. Significant amounts of research have shown that family and social supports are associated...
with psychological adjustment in a variety of medical populations. Griffith and colleagues report that diabetic patients with poor social supports show poorer diabetic control when under high stress than those patients who have high social support.26 Patients with poorer social supports and limited coping abilities generally have poorer psychosocial adjustment.27 Patients who avoid problems or emotions show greater levels of depression, anxiety, and psychopathology.28 Grassi and Rotti note that patients with an externalized locus of control—that is, those who perceive their life as controlled by forces outside of themselves—feel unempowered.29 As a result, these people have a greater experience of stress, have poorer coping abilities in general, have poorer social supports, and demonstrate greater psychological symptoms. They further point out that patients with increased psychiatric difficulties report increased adverse life events. This then can become a self-perpetuating problem.

**General Interventions.** Interventions must attempt to address those factors noted above. Pain and physical problems should be minimized. Metabolic abnormalities and medication side effects should be corrected to the extent possible. Efforts to improve health perception should begin well before transplant. These efforts include conveying a hopeful but realistic outlook, advocating self-efficacy, and involving the patient and family through education. This support can improve patient compliance, a direct reflection of self-efficacy.30 In the post-transplant phase, ongoing patient and family education about the medical, surgical, and psychological aspects of the process is also necessary. Goals should be set at attainable levels. The ‘art’ of goal-setting must take into account a patient’s motivation. Motivation can be considered as being either intrinsic—that is, as occurring from within one’s self—or extrinsic. Those people with greater degrees of intrinsic motivation are more internally driven and are often challenged by tasks and show greater perseverance to master them. It is these patients who probably have improved health perceptions at baseline, along with a greater sense of confidence, and may handle challenges with greater ease and lesser levels of intervention. Patients with greater degrees of extrinsic motivation rely primarily on their environment for motivation. These patients generally have lower self-esteem, lesser levels of confidence and a lower sense of self-efficacy and mastery. They become more discouraged when they are unable to accomplish tasks. It is possible, however, for these patients to develop more intrinsic motivation when they are involved in tasks and feel adequate enough at handling them.31 This means breaking down the large goal of returning to a pre-morbid level of functioning into many small goals. The emphasis is on attainment of these small goals in a progressive fashion and not on overall mastery. Physician recognition at each step is important. This can help increase the sense of self-efficacy, in turn improving health perception and increasing the likelihood of better adaptation. Exercise and adequate nutrition should be routinely recommended.

Acknowledgment of the feelings encountered by patients and families, especially anger and fear, is important. To the extent possible, these should be normalized as a part of the process—this can help patients to not feel alone with their struggles and to not take things as their fault. Because these feelings can give rise to lowered esteem, their recognition must be balanced with a focus on how to handle their feelings, on the achievements already made and on the goals ahead. Patients who have trouble controlling the expression of their feelings may respond to suggestions to channel their energy into physical avenues such as exercise—in addition, counseling may be necessary. For those patients who do not readily express their emotions, it is useful to ask about their feelings while normalizing the presence of a range of emotions as part of the process. Apprehension may respond to support, including regular office contacts. Advocacy for realistic environmental adaptations can be helpful. Finally, counseling/psychotherapy should be considered in patients who have a history of significant premorbid coping or personality problems, poor social supports, very long pre-transplant illnesses, or high levels of anger and hostility. Patients and families who do not respond to other interventions should also be referred for therapy.

**Employment.** Wide variability exists in the literature regarding return-to-work rates in post-transplant patients. Robinson found that 39% of post-transplant patients were working full-time three years after transplant.32 Esquivel found that 33% of post-liver transplant respondents were working full-time after transplant.33 And Ide reported 56% were employed one year following liver transplantation.34 Payne stated that many of their post-liver transplant patients were fully rehabilitated to the workplace after
Once transplant has occurred, continued positive reinforcement can impact perceived functioning and health status, as can appropriate goal-setting regarding return-to-work.

It is likely multiple pre- and post-transplant factors play a role in this variability. As expected, better levels of mobility, energy, sleep and emotional functioning pre-transplant predict more favorable return-to-work rates and resumption of hobbies at three months after transplant.\(^{37}\) Thomas suggests also that successful return-to-work depends on the nature of the work—the greater the flexibility in work schedule and duties, the greater the likelihood of successful return. Further, the nature of the disability/health insurance coverage during convalescence may be a factor—due to the necessity of medical follow-up and multiple ongoing medications, adverse changes in benefits that might occur at the time of return-to-work may adversely impact successful employment reintegration.\(^{38}\) Hunt notes that the presence of post-transplant complications is not a predictor of successful reintegration but, as in QoL research, the recipient's perception of their level of functioning appears to play a role. In addition, patients with good perceived physical function have more favorable return-to-work rates, regardless of objective functional abilities. Similarly, patients with perceptions of poor physical functioning appear to have more difficulties in returning to work despite normative actual physical function.\(^{39}\)

Finally, post-transplantation return-to-work is positively correlated with the pretransplant employment history.\(^{40}\) The focus for interventions is similar to those noted above, and begins in the pre-transplant phase. Efforts to preserve pretransplant job function can be helpful. Some patients may seek disability sooner than expected. This may be due to undiagnosed functional impairment, a sign of family coping difficulties, or an exacerbation of general pre-morbid coping problems. When it appears that such a request is a part of a history of coping difficulties, the reliance on disability should be minimized. Some patients, on the other hand, may resist the need to decrease their level of function. These patients may need encouragement to rest as necessary. Providers should educate patients and families on the post-transplant value of balancing optimum work function with adequate rest. Positive reinforcement and praise for adaptive functioning is important. Providers can consider working with their patients and their employers to help adapt job duties as necessary.

Once transplant has occurred, continued positive reinforcement can impact perceived functioning and health status, as can appropriate goal-setting regarding return-to-work. Recognizing achievement of these goals creates a positive focus over time and can help increase a sense of progress and competency, which in turn improves perception and further function. Efforts to advocate for appropriate workplace adaptation should continue.

**Social/Family Functioning.** The data in this realm is not clear about post-transplantation level of social and family functioning. Hellgren found that patients return to a level of function similar to that of a general population sample but Littlefield found diminished functioning compared to a general population sample.\(^{41}\) Tarter (1991) found that liver recipients demonstrated improved social functioning with less burden of illness on their families and social systems compared to pretransplantation, but lesser levels of function compared to a general population sample.\(^{42}\) Heyink found that a third of liver recipients were still experiencing difficulties gaining their pre-transplantation roles after an average of three years post-transplant.\(^ {43}\) This may be because difficulties that arise prior to transplantation, such as financial stresses, disruption of valued relationships, and significant anxiety and guilt make it more difficult to return to a pretransplant level of function. Payne found that family, social environment and relationships with the medical community were not significantly improved in transplant patients due to improvements that already occurred in these areas during the pretransplant illness.

Interventions in this realm parallel those already noted. Education about all aspects of the transplant process, including anticipated role changes, is important. Families that worry that the healthy recipient remains too ill should be countered with education. Families who return to a pre-illness lifestyle before the recipient is ready, may respond to a process of setting gradually increasing functional goals. Referral to a mental health provider should be considered in cases of ongoing difficulties.

**Psychiatric/Psychological Difficulties.** The prevalence of such difficulties appears to be generally similar to the general population. Lowe, Hellgren, and Collis each found the incidence of psychiatric difficulties in transplant patients to be the same as the general population. Dew found that one third of post-cardiac transplant patients showed high levels of distress one year after surgery and Heyink found one third of liver transplant patients had depression.
The prevalence of [psychological] difficulties appears to be generally similar to the general population.

Surman found 24% of liver transplant patients required treatment for depression. Commander found 18.8% of liver transplant candidates had a psychiatric disorder, comparable to the general population. And, Stilley noted that pretransplant psychiatric difficulties predicted post-transplant psychiatric difficulties. In addition to these general findings about psychiatric difficulties, it is worthwhile to discuss specific psychiatric syndromes, including cognitive changes, medication-induced difficulties, depression, anxiety and compliance problems (Table 1).

Cognitive difficulties. Pre-transplant cognitive difficulties may arise as the result of the illness that brought about the need for transplant in the first place—for example, alcoholism that caused the liver disease may also be the basis of a dementia—or can arise as a result of the metabolic changes that occur when organs progressively fail. While these changes may remit completely with the return of health after transplantation, Tartar notes these impairments may improve but do not necessarily disappear even after three years. The reasons for this are unclear.

Patients who show ongoing cognitive problems after transplant should be thoroughly evaluated for possible reversible disorders, including thyroid and other metabolic abnormalities, nutritional deficiencies, and medication side effects. If no basis is found, patients should be referred to a neuropsychologist for testing. The testing report should outline both the nature of the deficits and include recommendations of compensatory strategies.

Medication-induced problems. Three commonly used immunosuppressants are prednisone, tacrolimus and cyclosporine. These anti-rejection medications may have psychiatric/mood disturbance side effects.

Prednisone. Psychiatric side effects include sleep disturbance, appetite increase, irritability, mood lability, euphoria, delirium, psychosis and perceptual abnormalities. These disturbances tend to be dose-related, occur early in treatment, and may be time-limited. Depression occurs in approximately 40% of patients who use prednisone, mania in about 25%, psychosis in 15% and confusion in about 10%.

There are several interventions for persisting prednisone side effects. If possible, the dose should be reduced. Selective serotonin reuptake inhibitors (SSRIs), such as sertraline, fluoxetine, paroxetine, nefazodone and citalopram, can also be considered, particularly for mood effects and irritability. These agents are inhibitors of the cytochrome P450 system, particularly of the 2D6 isoenzyme system. Sertraline is a less potent inhibitor than fluoxetine, which is about equal to or somewhat less potent than paroxetine. Important medication interactions include the potentiation of calcium channel blockers, cimetidine, beta-blockers, opiates, antiarrythmics, oral hypoglycemics, cyclosporine, benzodiazepines (except lorazepam and oxazepam) and theophylline. Nefazodone primarily impacts the 3A4 isoenzyme system, and as such may potentiate steroids, digoxin, HMG-CoA reductase inhibitors and protease inhibitors, but is not known to increase cimetidine or theophylline levels. It has been known to rarely increase immunosuppressant levels. Citalopram is a weak inhibitor acting primarily in the 3A4 and 2C19 systems. It can potentiate the effects of cimetidine and beta-blockers. Dosing of any of these should be reduced in the presence of renal or hepatic dysfunction.

Other interventions include low dose antipsychotics for psychotic-like symptoms. An important consideration in using these is the effect of lowering the seizure threshold in patients who are on immunosuppressants, some of which also lower seizure threshold. Haloperidol and molindone are two of the standard antipsychotic medications that may have lesser impact on the seizure threshold, and olanzepine is a newer medication that can be considered. Mood stabilizers may be cautiously considered for significant affective lability. These include gabapentin, valproate, carbamazepine, and lithium. Gabapentin is the newest of these. It is excreted unmetabolized by the kidney, and dosing depends on renal function. Medication interactions are minimal. Valproate may adversely affect liver function so its use must be very carefully considered in patients who have undergone liver transplantation. Carbamazepine carries the risk of agranulocytosis, which makes this an uneasy choice in these immunocompromised patients. And both valproate and carbamazepine interact readily with various medications. Finally, lithium can adversely impact renal function and its level is easily impacted by diuretic use, medications that effect renal tubular function, fluid management strategies and dietary changes in sodium intake.

Tacrolimus. The possible neuropsychiatric side effects of tacrolimus include anxiety, tremor and delirium. The incidence of these is unknown.
In post-liver and heart transplant patients the incidence of depression is comparable to the general population. . .

While these side effects can occur at high blood levels, they can also occur at normal levels. An MRI scan of the head may be useful by demonstrating characteristic hyperdense regions.

Interventions include reducing the level if possible, changing agents, or using SSRIs or low-dose antipsychotics.

Cyclosporine. Possible neuropsychiatric side effects include delirium, speech difficulties ranging from apraxias to mutism, a reversible leukoencephalopathy that includes headaches and altered mental status, cerebellar symptoms, extrapyramidal symptoms, peripheral neuropathies and visual difficulties including cortical blindness. Incidence of these has been estimated to range between 0.5%-35%. MRI scans of the head may or may not show hyperdense regions.

Interventions include dose reduction if possible, changing agents or use of low-dose antipsychotics.

Depression. Depression is a term commonly used by the general population to describe a variety of feelings and conditions, including sadness, loss, anger, bereavement and upset. However, psychiatric syndromes of depression have specific sets of symptoms and are different from “normal” sadness, upset or bereavement. DSM-IV outlines the criteria for the major affective syndromes.48

Major depression includes five or more of the following symptoms that must be present for at least two weeks: daily low mood, anhedonia, weight and appetite changes, sleep changes, agitation/slowing, fatigue, worthlessness/guilt, reduced concentration, or suicidal ideation. Symptoms may vary in a culturally-related fashion. Further, to qualify as a major depression, the symptoms may not be due to a medical condition or medication. It is about twice as common in females than males in the general population, and is most likely to occur between the ages of 25 and 44. The point prevalence ranges between 2% and 9% in the general population. In post-liver and heart transplant patients the incidence of depression is comparable to the general population according to Stilley. Of interest, Mai, Bart, and Reithar note that pretransplant depressive symptomatology decreases post-transplant in heart, liver and lung recipients.49-51

If the depression is due to one of the immunosuppressant medications, its dose should be reduced or the agent changed. If these are not possible, standard antidepressant treatment is used. SSRIs should be considered. Ritalin may also be of help and will show a more rapid response than the SSRIs, which take approximately 4 weeks to begin showing a response. As necessary, patients should be referred for counseling/therapy.

Anxiety. Anxiety is a normal human response to perceived threat. Threats can come from the external environment but may also come from one’s internal environment, the psyche. Patients with lesser psychological abilities tend to be more easily threatened and, as such, may experience increased levels of anxiety and appear more defensive. Those with better psychological skills tend to be more resilient to stresses and threats. Anxiety symptoms

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Post-transplant anxiety can be due to emotional reactions to some aspect of the transplant process, to medication side effects, or may represent a specific anxiety syndrome.

Panic disorder. Panic disorder is characterized by discrete periods of fear or discomfort in which four or more of the following are experienced abruptly and peak within 10 minutes: palpitations, accelerated heart rate, sweating, trembling, shortness of breath, feeling of choking, chest pain/discomfort, nausea/abdominal distress, dizziness/lightheadedness, derealization, fear of losing control or going crazy, fear of dying, parasthesias, or chills/hot flashes. It may occur with or without agoraphobia—that is, anxiety about or avoidance of situations from which escape may be difficult or help may not be available. It is 2-3 times more likely in women than men in the general population, and the age of onset is typically before 45. The one-year prevalence rate is between 1-2%. Of note, major depression occurs in 50-65% of patients who have panic disorder.

Panic disorder usually responds to benzodiazepines, SSRIs, or tricyclic antidepressants. Benzodiazepines work rapidly and can be used on an as needed basis or as standing dose medications. Several factors are important to consider in using benzodiazepines. The use of these in an as needed fashion can provide patients with a greater sense of control over their situation but may contribute to an escalating cycle of greater anxiety or pain. This can occur because such use of the medication depends first on the patient's experience of the symptoms to signal the need to take the medication. By then, the anxiety or pain may be significantly heightened, requiring greater doses of the medication. This in turn increases the likelihood of greater apprehension about the next experience of the anxiety. Standing dose use may obviate this cycle but patients will develop tolerance if used regularly over 3 to 4 weeks. At that point, compliance is key since abrupt discontinuation may lead to withdrawal symptoms including seizures. The use of benzodiazepines should be minimized in patients with a history of alcohol or substance abuse. If used in such patients, careful monitoring of prescription patterns is necessary. Dosing should be reduced in the presence of renal or hepatic impairment. Among the benzodiazepines, the use of lorazepam or oxazepam can be considered since these are metabolized via glucuronidation and have no active metabolites.

Post-traumatic stress disorder. This diagnosis requires that a person has been exposed to a traumatic event that involved actual or threatened death or serious injury, and that the person's response involved intense fear, helplessness or horror. In addition, the person must manifest three or more of the following: a subjective sense of detachment or numbing, a reduction in awareness of their surroundings, derealization, depersonalization, or dissociative amnesia. Further, the event must be persistently re-experienced and the person must show intense avoidance of the event or associated stimuli. There must also be significant distress and psychosocial impairment. There are persistent symptoms of arousal, which can include difficulty falling asleep, outbursts, difficulty concentrating, hypervigilance or exaggerated startle response. The duration of symptoms is greater than one month and they typically occur within 6 months of the stressor. Symptoms may become chronic. The lifetime prevalence has been estimated to range from 1-14% in the general population.

Interventions involve medications and counseling. Antidepressants—both SSRIs and tricyclics—may be useful with a variety of the symptoms. Benzodiazepines can be used for anxiety, and beta-blockers may have a role for the increased arousal. Also, antipsychotics and mood stabilizers may be used for psychotic-like symptoms and affective lability, respectively. Counseling/psychotherapy is a key aspect of treatment, and patients should be referred to a mental health provider.

Generalized anxiety disorder. Symptoms of this disorder include excessive worry and anxiety most days for at least 6 months that impairs functioning.
Problems adhering to medication regimens or appointment schedules greatly increase the risk of organ rejection.

The anxiety is difficult to control and does not have a specific focus. At least three of the following symptoms are necessary for the diagnosis: Restlessness/agitation, easily fatigues, difficulty concentrating, irritability, muscle tension, or sleep disturbance. The sex ratio is about two-thirds female, and the 1-year prevalence is about 3% in the general population.

Interventions for GAD often involve medications—SSRIs, benzodiazepines, and buspirone. In addition, behavioral techniques are helpful for some. Patients who find limited success with these treatments should be referred for psychotherapy.

Compliance. Compliance issues are of significant importance in transplant patients. Problems adhering to medication regimens or appointment schedules greatly increase the risk of organ rejection. Littlefield shows that one-fourth of transplant patients had trouble with medical adherence. Schweitzer found that compliance problems were implicated in 91% of graft failures in a renal transplant population. Side effects can impact medication compliance. Poor compliance may be a reflection of coping problems in other life areas, or may be a reflection of an acute psychiatric problem. Many authors suggest the presence of a personality disorder increases the chance of noncompliance in the post-transplant period.27,54-58

It is one’s personality, a mix of inborn factors and learned responses, that determines how one interacts with the world. Personalities run the gamut from highly adaptive and flexible to highly maladaptive and inflexible. While everyone at times uses lesser adaptive coping skills, a longstanding pattern of maladaptive abilities over many different situations suggests the presence of a personality disorder. Very often, those with personality disorders have difficulties in their relationships, are more readily susceptible to stresses, and may have poorer esteem. It is important to note that not all patients with personality disorders will have compliance problems.

Interventions for compliance problems begin with careful pretransplant screening of patients for risk factors for non-compliance—pretransplant compliance behaviors can be predictive of post-transplant behaviors. Once listed, education of the patient and family about the post-transplant follow-up regimen, medications and possible side effects is necessary. After transplant, re-education is useful. Also, helping patients and families problem-solve side effects and emotional reactions may be of value. Primary care physicians are in a unique position to help with these things because of their understanding of their patients over time—Christensen suggests that interventions which may help adherence are those which are tailored to fit both the specific patient and that patient’s specific treatment situation.59 As necessary, external supports should be increased. In some cases this may be as simple as the use of a medication box to organize medications; in other circumstances, the use of visiting nurses may be warranted. Treatment of any underlying psychiatric difficulty, including substance abuse, is necessary. Finally, patients should be referred for counseling/psychotherapy.

Summary

The well transplant patient faces significant psychological challenges in returning to health. The challenges to adapt begin long before transplant with the struggle to cope with the fears that accompany serious threats to health and role function. Loved ones are also called upon to face these challenges. QoL often improves after transplant. Primary care providers have a valuable role in assisting patients and their families through the provision of ongoing support; by helping them appropriately express their fears, anger, and anxieties; by educating them all along the way; and by setting attainable goals and praising their achievement of them. Psychiatric difficulties that arise can include cognitive difficulties, psychiatric side effects of the immunosuppressants, depression, anxiety and non-compliance. Providers can address these through a variety of interventions, including referral to mental health professionals.


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