

Review Article

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Organ transplant & the psychiatrist: An overview

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Organ transplantation has emerged as the saving grace for those who are suffering from end organ disease. Advent of modern surgical procedures and immunosuppressants further decrease morbidity and mortality. Meta-analyses have shown that post-organ transplantation quality of life improves for social, physical and daily activity functioning, but not consistently for psychological health. Psychiatrists can play a useful role not only in selecting the best suitable candidate for the procedure by psychosocial screening but also to tackle post-operation psychological issues that trouble patients as well as caretakers and decrease their quality of life. Issues like selection of patients with psychiatric disorders and substance abuse for transplantation process and their treatment both pre- and post- operation, risky health behaviours, treatment adherence for immunosuppressants and psychological support for caretakers can be better addressed by a psychiatrist who is sensitive towards these issues. Prescribing various psychotropics and immunosuppressants in the background of impaired organ function and drug-drug interaction is further challenging. Thus, psychiatrists need to be knowledgeable about these issues and should be an integral part of organ transplantation team for overall better outcome.

Key words Organ transplantation - psychiatrist - psychiatric disorders - quality of life - substance abuse

Introduction

Organ transplant/transplantation (OT) has been defined as the therapeutic grafting of an organ from a living or dead body to a living body¹. OT is a complex, invasive and major surgical procedure which carries tremendous expectations from the OT candidates and caregivers for saving life and improving the quality of life (QOL). Thus, starting from the onset of the end stage organ disease (ESOD), undergoing evaluation for candidacy, surgical procedure and related complications, and ending with death, all through these phases OT and organ donation are inherently

enormously distressing. Also, OT is bound to ethical and legal issues. In the developing countries, the picture gets complicated by the psychosocial milieu being different in terms of poverty, underdeveloped protective medical institutional mechanisms, family structure and functioning, cultural norms and values related to organ donating/receiving. Emerging evidence shows that pre-operative psychosocial variables can predict post-transplant psychiatric adjustment for most organ types², and meta-analyses have shown that post-transplant QOL improves for social, physical and daily activity functioning, but not

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consistently for psychological health^{3,4}. This implies that while medico-surgical teams take better care of the physical health, they may leave out the psychological perspective. The medico-surgical teams may overlook psychological distress, especially if underplayed by the subjects.

This overview highlights the psychiatrist's perspective on psychosocial and medication issues related to the organ recipients, donors, and caregivers, and their effect on the OT outcome. The aim is to highlight the role of the psychiatrist and to sensitize the medical fraternity in general and the OT teams in particular. The literature search strategies included electronic databases and manual searches of relevant publications or cross-references. Electronic search included PubMed and other search engines (Embase, Science Direct, Google Scholar) for the years 2005-2014. Cross-searches often yielded additional relevant material. The search terms used in various combinations were: transplantation, psychiatrist, psychiatry, living donors, caregivers, psychotropics. The relevant articles were selected based on their importance for psychosocial and psychiatric aspects of OT. Accordingly, we selectively focussed on good and large scale relevant reviews and meta-analyses. Thus, this review attempts to give an overview of the area and is not a systematic review of the area⁵. Relevant Indian research is summarised separately.

Organ transplant: A heavy burden

Organ transplant is a continuum of different phases, each associated with its own individual, social and economic problems.

(i) End stage organ disease (ESOD) is the patient's worst clinical state with failed organ function. As a matter of life and death, it marks the beginning of OT.

(ii) OT evaluation involves various steps to achieve OT candidacy, at the cost of a performance anxiety and the fear of omission.

(iii) Waiting for organ donation is the most distressing phase. Continued deterioration of health and critical medical care like dialysis is associated with 10-18 per cent patients dying, and 5 per cent becoming medically unsuitable; another 2 per cent refuse OT⁶. The greatest obstacle is the shortage of donated organs; in the USA 40 per cent candidates wait for >2 years before they get an organ⁶.

(iv) Transplantation and after, means dealing with a complex OT procedure, perioperative complications, and a post-OT life with constant threat to survival, and inevitable and often distressing dependence on caregivers for help on various counts.

Unique dual role of psychiatrist in transplantation

Comprehensive pre-transplant psychosocial evaluation helps to get a more complete understanding of mutual, and sometimes contradictory, expectations and needs of transplant candidates, donors, caretakers and the transplant team. The psychiatrist plays a unique dual role in serving both the needs of the transplant team as well as the transplant patient, donor and the carers⁷. The psychiatrist also has a major role in identifying problematic areas/issues both pre- and post-transplant and address those to seek improved outcomes.

Pre-transplant psychosocial evaluation

It is a stepping stone for OT candidacy. Limited availability of donor organs, need for psychological sophistication, good family support, considerable medical and financial resources for better care and outcome - all dictate the selection of only those candidates who have the best chance of post-OT outcome. To select the best candidate for transplantation, there is a need to screen the patient's coping skills for stressors, co-morbid psychiatric conditions and their pre- and post-transplant monitoring and treatment, capacity to understand the transplant process and to provide informed consent, ability to collaborate with the transplant team and to adhere to treatment, substance use/abuse history, recovery, and ability to maintain long-term abstinence, health behaviours that may influence post-transplant morbidity and mortality like eating or exercise habits, level of social support available to the candidate for pre- and post-transplant phases and psychosocial needs of the patient and family and plan for services during the waiting, recovery, and rehabilitation phases of the transplant process⁸.

Some of the important aspects of organ transplant will be considered in the following sections which demand a psychiatrist's expertise:

Treatment adherence

Treatment adherence generally includes regular intake of medications, monitoring vitals, undergoing diagnostic tests, following dietary and exercise protocols, abstinence from substance abuse, and regular

follow up. A meta-analysis of 147 studies across all organ types showed average non-adherence per 100 PPY (persons per year) to be 1-4 for substance use, 19-25 for immunosuppressants, diet, exercise, and other requirements⁹.

A review of 17 studies showed non-adherence to be associated with poor clinical outcome, contributing to 20 per cent of late acute rejection episodes, lower number of quality adjusted life years and lower lifetime costs because of shorter survival¹⁰. Thus, it is very essential to identify candidates with ambivalence about treatment and prior history of non-adherence, substance abuse, poor social support, and poor organisational skills as they are more prone for treatment non-adherence.

Risky health behaviours

These include substance abuse, poor eating habits and sedentary lifestyle leading to obesity. Studies have shown that pre-transplantation BMI >30 kg/m² or body weight >140 per cent of ideal, decrease survival rate among transplant recipients compared to controls among renal¹¹ and heart¹² cases, respectively. Another study showed that compared to controls nutritional counselling of OT subjects, once weekly for a month and once monthly for next three months, reduced post-transplant weight gain¹³. Presumably poor outcome may be reduced by identifying reasons and risk factors for non-adherence and risky health behaviours, educating patient and family members regarding the same, making plan for monitoring both pre- and post-OT, and written informed behavioural and contingency contracting making the patient responsible for own acts. Recently, efforts have been made to develop a programme based on prevailing evidence to promote self-management skills for behaviours such as undesired weight gain, exercising and smoking¹⁴.

Psychiatric disorders among OT cases

Like other chronically medically ill subjects, OT cases are also at higher risk for psychiatric disorders. It may be due to either the exacerbation of a pre-existing disorder or the development of new-onset disorder. With no large-scale prevalence rate comparisons yet available, no strong evidence exists that in OT the rates of psychiatric disorders vary by the organ.

Mood and anxiety disorders

Anxiety or depressive disorders are experienced by 25 per cent of lung, 40 per cent of liver and 50 per cent of heart pre-OT cases¹⁵. In post-OT cases during the first several years, major depression was experienced

by 20 per cent of kidney, 30 per cent of liver, and 63 per cent of heart cases. Compared to pre-OT/waiting period the risk was greatest in the first post-OT year; contributing factor being the stress associated with physical recovery, rehabilitation, adaptation to immunosuppressive medications, and psychosocial role change^{16,17}. Studies have shown that while the patient is in waiting period depressive symptoms are associated with poor QOL, poor adaptive coping, and low functional status, and there is high mortality in patients with depressive symptoms both during pre- or post-transplant period¹⁸⁻²⁰.

Among anxiety disorders during OT, post-traumatic stress disorder (PTSD) is most important: 14-44 per cent of ICU-treated cases experience PTSD, with >24 per cent having persistent symptoms years later²¹. PTSD may result from any medical crisis during waiting period, surgery itself, and hallucinations and delusions associated with post-surgical delirium²². Post-traumatic stress disorder or symptoms are shown to increase mortality, decrease QOL and life satisfaction^{23,24}. With mood and anxiety disorders conclusively predicting higher morbidity and mortality, 45 per cent of OT centres in the USA consider current affective disorders as an absolute contraindication for OT²⁵.

Psychotic disorders

Psychosis emerging beyond post-operative recovery period occurs exclusively in OT cases with past history of such illness. Among such cases, 37 per cent experienced manic or psychotic episodes in the first several post-OT years²⁶. Hence, there is a need for aggressive pre-OT treatment as psychotic symptoms have a negative impact on OT outcome. However, it remains debatable as to how fair it is to deny organ to a psychotic patient; in the USA, 92.3 per cent OT centres consider active schizophrenia as an absolute contraindication for OT²⁵.

A survey across 12 OT centres in US, Canada and Australia showed non-compliance with immunosuppressant drugs among psychotic cases living alone to be 45.5 per cent, 9.5 per cent among psychotic cases living with someone, and 20-50 per cent among overall OT cases. Suicide attempts in the pre-OT year were recorded in 35.7 per cent cases with psychotic symptoms versus 5.9 per cent of those without psychotic symptoms²⁶. Thus, it is evident that in cases with psychosis, good social support and adequate pre-OT symptom control mean a better outcome.

Personality disorders

The OT process demands a series of adaptations in physical and social functioning and ability to cooperate with caregivers and OT team. The persisting and inflexible maladaptive patterns of behaviour with personality disorder (PD) cases lead to impaired interpersonal relationship and social functioning.

Incidence of personality disorders among OT cases has been reported to be 10-26 per cent, similar to that in general population^{27,28}. A survey of all active OT programmes in the USA showed that 14.1 per cent of heart, 8.7 per cent of liver, 5.2 per cent of kidney OT programmes viewed personality disorder as an absolute contraindication to OT²⁵. Another study showed that borderline personality disorder carries highest risk for post-OT non-compliance, less stable social support and strained working relation with OT team²⁹. In a study in alcoholic liver disease cases with anti-social personality disorder, 50 per cent returned to either alcohol or narcotic addiction compared to 20 per cent with no personality disorder³⁰.

Cognitive disorders

Through pre- to post-OT phases, cases frequently experience reductions in cognitive functioning ranging from subclinical to frank delirium. Among OT recipients cognitive impairment remains relevant in terms of potential negative impact on treatment compliance due to patient's inability to learn old or new instructions/regimens for medication, investigations and behaviours related to memory deficits, delusions and hallucinations associated with delirium. Perhaps due to these facts dementia is considered as an absolute contraindication among 72 per cent of the US OT centres²⁵.

Mental retardation (MR)

There is no scientific evidence suggesting cases with MR should not have access to organ transplantation. Yet, 25.6 and 74.4 per cent OT centres in the USA considered IQ 70-90 and IQ <70, respectively as an absolute contraindication for transplantation²⁵. This automatic exclusion of cases with MR from OT continues to be a matter of debate as a clear form of discrimination. A review of cases with MR and renal OT showed post-OT survival rates of 100 per cent at one year and 90 per cent at three years³¹. These rates were similar to those of non-MR cases. This review highlights that adequate support from family and other caregivers rather than the recipient's IQ level predict post-OT medication compliance³¹.

Substance abuse

In both the USA and Europe the most common indications for liver transplantation are cirrhosis due to alcoholic liver disease (ALD) and hepatitis B and C (HBV, HCV), especially among intravenous drug abusers. The OT teams continue to debate whether or not to offer OT to cases with substance abuse. The major concern is post-OT substance abuse relapse resulting in direct damage to transplanted organ, decreased efficacy of ongoing medical treatment, increased risk for cancer and non-adherence to treatment; all eventually leading to graft failure and recipient death³².

Tobacco use in immunosuppressed patients increases risk of cancer³³. Smoking increases vascular complications among post-OT liver cases (17.8% in smokers vs. 8% in controls)³³. In ALD liver transplant recipients, risk of oropharyngeal and lung cancer was 25 and 3.7 times higher compared to controls³⁴. Another study showed transplanted ALD cases had 1- and 5-year survival rates of about 80 and 70 per cent, respectively, comparable to transplants for other causes of cirrhosis³⁵. Though there is sufficient evidence to suggest post-OT substance use carries major adverse health consequences, a meta-analysis of 54 studies showed post liver OT relapse to any alcohol use twice more than relapse to heavy alcohol use (~6 vs <3/100 PPY) and non-adherence to immunosuppressant medication being 3.2/100 PPY. These figures are comparable to cases with no prior history of abuse³⁶. The pre-transplant history of illicit drug use has not been consistently shown to be associated with increased risk for post-transplant alcohol relapse in ALD recipients³⁷⁻⁴², possibly because many ALD recipients had discontinued their drug use many years prior to transplantation³⁷. Thus, a history of substance abuse should not be an absolute contraindication for OT. The available research shows cases with history of alcohol abuse that are treated effectively have relapse rate, non-adherence to medications, and survival rates comparable to cases with no such history³⁸. More worrying is relapse to tobacco use and associated medical complications. Smoking, both by donors and by recipients, has a major negative impact on outcomes after organ transplantation⁴³. The risk factors for relapse include poor social support, family history of alcohol dependence, pre-transplant abstinence of ≤ 6 months, past failed rehabilitation, and multiple substance abuse.

There are no efficacy studies on treatment. General advice is for frequent follow up with random

toxicological screening, motivation enhancement therapy (MET), and relapse prevention counselling (RPC). Among medications, naltrexone being a direct hepatotoxin, is contraindicated in liver failure. Disulfiram is hepatically metabolized and may lead to immunosuppressant toxicity. Selective serotonin reuptake inhibitors (SSRI) and tricyclic antidepressants (TCA) improve abstinence rates in depressed relapsing alcoholics⁴².

Immunosuppressant related neuropsychiatric manifestations

Common immunosuppressants currently used in OT (tacrolimus, cyclosporine, corticosteroids, azathioprine and mycophenolate mofetil), are all well known for their neuropsychiatric side effects.

Calcineurin-inhibiting immunosuppressants(CII): Tacrolimus and cyclosporine have a similar neurotoxic profile: 40-60 per cent recipients have mild symptoms like tremulousness, headache, restlessness, insomnia, vivid dreams, photophobia, dysesthesias, anxiety, and agitation, and 20-32 per cent have moderate to severe symptoms like cognitive impairment, coma, seizures, focal neurological deficits, dysarthria, cortical blindness, psychosis, and delirium. With discontinuation of CII, most of the side effects resolve spontaneously. Short term anticonvulsants can be used for CII-induced seizures, and benzodiazepines or beta-blockers for anxiety, tremor, or restlessness⁴².

Corticosteroids: High dose corticosteroids are usually given immediately post-transplantation and for initial treatment of rejection. Steroid induced psychiatric syndromes are common, complex, unpredictable, and range from subtle mood changes to full blown affective syndromes and frank psychosis. Mild symptoms of agitation, anxiety, distractibility, fear, insomnia, lethargy, labile mood, and restlessness occur in 20-30 per cent and severe symptoms of affective syndromes, psychosis and cognitive impairment in six per cent cases⁴⁴. Treatment includes steroid dose reduction or discontinuation. If steroid dose reduction is not feasible, symptomatic treatment with antipsychotics, mood stabilizer or anti-depressants is recommended⁴⁴.

Azathioprine: There are reports of depressive symptoms induced by azathioprine in combination, with cyclosporine and prednisone in particular⁴².

Mycophenolate mofetil: CNS adverse effects- anxiety, depression, delirium, seizures, agitation, psychosis and somnolence - have been recorded in 3-20 per cent recipients of mycophenolate⁴².

Management of psychiatric disorders

The risk for psychiatric disorders rises during organ transplantation and it adversely affects the OT outcome, compliance, morbidity, and mortality. Patients with mental health disorders, when adequately controlled and socially supported, have outcomes similar to the general transplant population⁴⁵. Hence, there is need for early recognition and management.

Psychotropics

Organ dysfunction during pre-transplant period changes the pharmacokinetics of psychotropic agents, requiring proper selection of the drug and the dose. Similarly in post-OT period, psychotropics selection is influenced by drug pharmacokinetics, adverse effects, and tolerability and drug-drug interactions. Studies on the treatment of psychiatric disorders in OT cases being limited, the decisions need to be based on a review of clinical and pharmacokinetic data⁴⁶⁻⁴⁹.

Selection of psychotropics in liver failure

Antipsychotics are mainly metabolized by liver except for sulpiride, amisulpride and paliperidone. In mild-moderate liver disease all antipsychotics can be tried with caution, but in severe liver disease it is better to avoid those metabolised by liver⁴⁹. All antidepressants are also mainly metabolized by liver. TCAs can cause sedation and constipation, and SSRIs can prolong prothrombin time (PT). Escitalopram with minimal effects on hepatic enzymes and sertraline with minimal drug-drug interactions are SSRIs of choice, although clinical experience is limited. Serotonin norepinephrine reuptake inhibitors (SNRIs) can be used with dose reduction. Mirtazapine with its minimal effect on CYP enzymes system is a better choice for patients with insomnia and anorexia^{46,48,49}.

Mood stabilizers except for lithium and gabapentin are metabolized by liver, alter liver function test, especially during the first month but it is transient⁴⁹. Benzodiazepines (BZDs) lorazepam, oxazepam, temazepam have short half-life with no active metabolites. So these are the better choice among BZDs⁴⁹.

Selection of psychotropics in renal failure

Antipsychotics except for amisulpride and sulpiride can be used in standard doses but with caution. Drugs with anticholinergic properties may cause urinary retention, confusion, and hypotension and ziprasidone with a potential to cause prolonged QTc interval are

better avoided⁴⁹. Among antidepressants, there is no preferred agent. In severe renal impairment and anuria, dose adjustment is indicated^{46,48}. Benzodiazepines are mainly metabolized in liver. In ESRD dose reduction is generally not necessary except for midazolam and chlordiazepoxide whose active metabolites are excreted through kidney⁴⁹. Among mood stabilizers, lithium is excreted unchanged in urine up to 95 per cent and is a known nephrotoxic. Also, being small molecule lithium is readily dialyzed and entirely eliminated by dialysis. If lithium is to be used in ESRD because of non-response to other mood stabilizers, single dose (usually 600 mg) treatment is recommended after each dialysis session. Other mood stabilizers can be used with caution^{48,49}.

Psychotherapy

Empirical data regarding psychotherapeutic interventions among OT recipients are very limited. Procedures that are commonly employed in clinical settings are group therapy, educational groups, support groups, internet based regimen and mentorship programme⁵⁰. A study has shown both individual and group psychotherapy to be beneficial and individual therapy to be better than group therapy. Both decrease the negative affect, increase happiness and QOL⁵¹. Another study showed telephone-based emotional support and cognitive behaviour therapy to increase QOL and social network⁵². Internet based intervention improved compliance, QOL, follow up care and decreased anxiety, depressive symptoms in both patients and caregivers among heart transplant recipients⁵³. Mentorship by an already transplanted recipient augmented patient care by providing information and support from a peer perspective⁵⁴.

Drug-drug interactions between immuno suppressants and psychotropics

Commonly used immunosuppressants like steroids, tacrolimus, cyclosporine and mycophenolate have narrow therapeutic index and are mainly metabolized by cytochrome P450 3A4. Specific cytochrome P450 3A4 inhibitors in decreasing order are: fluvoxamine, nefazodone>fluoxetine>sertraline, TCAs, paroxetine >venlafaxine⁵⁵. There are many case reports of tacrolimus and cyclosporine toxicity, when fluvoxamine and nefazodone were added to treat depression⁵⁵. In contrast, many case reports favour safe use of other antidepressants in combination with immunosuppressants. Cyclosporine increases lithium resorption by proximal tubule, so it is mandatory

to monitor lithium level in patients on cyclosporine. Disulfiram may interact with the alcohol vehicle of cyclosporine and its active metabolite is an inhibitor of CYP450 3A4⁵⁵.

Burden among caregivers

Dependency of transplant recipients on caregivers for everything including self-care, treatment adherence, finance, transportation, and emotional support, put them under stress. Heavy burden on caregivers and negative coping styles are shown to be associated with higher levels of depression⁵⁶. In a study on caregivers of lung OT cases stress related depressive and anxiety symptoms have been reported in 82 per cent caregivers. Acute illness stage was rated more stressful than rehabilitation stage. Compared to spouses, mothers were particularly vulnerable as support persons⁵⁷. Another study on heart transplantation group showed employment status and caregivers' physical health as strong predictors of post-OT distress. Increased distress was noted in early post-OT but not in later months⁵⁸. In a study on renal OT group, all caregivers perceived burden, more if the patient was a male⁵⁹. There was no relationship between caregiver burden score and patients' marital status, education level, operation time, age, donor type (cadaveric or living)⁵⁹. The data regarding intervention studies are lacking; the available data show group therapy, support group and web based interventions as useful strategies in alleviating distress among caregivers.

Issues of living donor

In view of the organ shortage living organ donation is an alternative to deceased organ donation. In the USA, related and unrelated living donors constitute 44 per cent of all organ donors. Of these, 95 per cent are kidney donors, four per cent are liver donors, and the remaining one per cent are pancreas, intestine and lung donors⁶. Donors with altruistic motivation, no ambivalence, good understanding about risks and benefits of donation, no history of psychiatric illness or substance abuse, good family support and financial stability are known to have better outcome. In a systematic review of 51 studies, 5139 living kidney donors assessed after four years showed that the majority experienced no depression (77-95%) or anxiety (86-94%), reported unchanged or improved relationship with the recipient (86-100%), and reported psychological benefits from donation in terms of gratification of helping the needy and experiencing increase self-esteem. Though most scored high on QOL measures, a small proportion

had adverse psychosocial outcomes⁶⁰. Another study reported a reasonable QOL among lobar lung donors, despite a subjective decline in exercise tolerance⁶¹. In a six month follow up study of 392 liver donors, 16 (4.1%) had one or multiple psychiatric complications [12 depression, 2 anxiety, 2 substance abuse, and bipolar affective disorder (BPAD), 1 accidental overdose, insomnia, crying episodes, and worsening of obsessive compulsive disorder (OCD) each]⁶². It was not clearly known if the donors were inherently more prone to psychiatric problems and had concealed this during evaluation or hepatectomy; or the psychiatric problems were a consequence of hepatectomy which is a more invasive procedure with more post-operative medical complications⁶².

Indian scenario

There is very limited research from India on psychiatric issues related to OT. An early study reported negative emotions among kidney recipients and donors. Among the recipients the common emotions included anxiety-depression and resentment during dialysis and perioperative period, and anxiety, dependency-frustration, body image change and decreased libido on a long term basis⁶³. Among the donors, hostility towards family members, ambivalence towards recipients, adjustment problem at work and with spouse, anxiety about surgical procedures were recorded pre- and during OT period and excessive worry about physical symptoms of recipients, depression and hypochondriacal symptoms post-OT⁶⁴. A study with live kidney donors showed their morbidity, mortality and QOL remained unchanged⁶⁵. Cognitive profile and depression were studied in 30 renal transplant patients which showed depression rate of 87 and 57 per cent one month before and three month after transplantation and mean IQ increased from 88.5 to 101 following transplantation especially with respect to concentration and visual organization⁶⁶. In a six month to six year follow up of 50 male kidney recipients psychiatric illness was noted in 46 per cent of patients and it was more common among unmarried, high education group and high socio-economic status⁶⁷.

Conclusion

Transplantation is a challenging process for patients, caregivers, and medical professionals. It is associated with substantial emotional distress with tremendous lifestyle changes and psychological stresses. Psychosocial evaluation, considered to be a gate pass for transplantation, carries great significance.

Depression and anxiety are the most common psychiatric disorders among the OT candidates and recipients. Currently, there is no general consensus on how to select/reject cases for transplantation with affective disorders, psychotic disorders, personality disorders and substance dependence. As the psychiatric disorders predict poor outcome both pre- and post-OT, it calls for an aggressive management. Immunosuppressants related neuropsychiatric side effects and drug-drug interactions with psychotropics should be kept in mind while treating psychiatric disorders. Caregivers also carry significant distress and need support. A psychiatrist as a member of the OT team can be of help for better outcome of OT.

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