ORIGINAL ARTICLE

Antidepressant medication use before and after kidney transplant: implications for outcomes – a retrospective study

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SUMMARY

We examined a novel database wherein national US transplant registry identifiers were linked to records from a large pharmaceutical claims warehouse (2008–2015) to characterize antidepressant use before and after kidney transplantation, and associations [adjusted hazard ratio (aHR) 95% CI] with death and graft failure. Among 72 054 recipients, 12.6% filled antidepressant medications in the year before transplant, and use was more common among women and patients who were white, unemployed, and had limited functional status. Pre-transplant antidepressant use was associated with 39% higher 1-year mortality (aHR 1.39, 95% CI 1.18–1.64) and 15% higher all-cause graft loss risk (aHR 1.15, 95% CI 1.02–1.30). More than 50% of patients who filled antidepressants pre-transplant continued fill post-transplant. Antidepressant use in the first year after transplant was associated with twofold higher risk of death (aHR 1.94, 95% CI 1.60–2.35), 38% higher risk of death-censored graft failure, and 61% higher risk of all-cause graft failure in the subsequent year. Pre-listing antidepressant use was also associated with increased mortality, but transplantation conferred a survival benefit regardless of prelisting antidepressant use status. While associations may in part reflect underlying behaviors or comorbidities, kidney transplant candidates and recipients treated with antidepressant medications should be monitored and supported to reduce the risk of adverse outcomes.

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Introduction

Transplant candidates undergo thorough evaluation to assess suitability for transplant. Psychosocial considerations include pre-existing mental health conditions, social support, and adherence history [1]. Depression is a common mental health condition, estimated to affect approximately 9% of Americans at any given time and ultimately 16% of the US population over a lifetime [2]. The prevalence of depression is higher among patients with chronic illnesses, including chronic kidney disease [2]. Although kidney transplant has been shown to improve quantity and quality of life compared with long-term dialysis [3], the implications of depression for kidney transplant-related outcomes are incompletely defined.

Prior studies have examined the prevalence, correlates, and outcomes associated with depression in transplant recipients, typically based on administration of survey instruments at single centers. For example, two studies reported lower depression rates after transplant compared with rates among patients on the waiting list [4,5]. Correlates of depression among wait-listed candidates and transplant recipients have also been described [4–6]. One study of billing claims among Medicare-insured kidney transplant recipients found that depression diagnoses were more common among recipients who were women, white, diabetic, and those with prolonged dialysis durations [7]. A diagnosis of depression in the first 3 years after transplant was associated with increased risks of graft failure and death with a functioning graft. Higher rates of post-transplant death in depressed patients have also been reported in single-center cohort studies [8,9].

Currently, the national US transplant registry does not collect measures of mental health comorbidity or treatments before or after transplant. However, linking the transplant registry with other data sources can combine the value of transplant recipient status, baseline clinical characteristics, and patient and graft survival records with additional outcome and exposure information. Pharmacy fill records offer nonobtrusive measures of prescribed health care that may serve as surrogate measures of comorbidity [10–13]. For mental health conditions such as depression, prescription data can identify patients with medically treated forms of the disorder.

We examined the frequency, correlates, and outcomes of antidepressant medication use as a measure of treated depression in a national sample identified by linking the transplant registry with pharmacy fill records. Using this integrated data source, we assessed associations of pre-transplant and prelisting antidepressant use with death and graft loss, persistence of pre-transplant antidepressant use patterns after transplant, and associations of antidepressant use in the first year post-transplant with subsequent adverse events.

Methods

Data sources

This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR system includes data on all transplant candidates, recipients, and donors in the USA, submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration (HRSA), US Department of Health and Human Services, provides oversight of the activities of the OPTN and SRTR contractors. Baseline demographic information ascertained for kidney transplant recipients at the time of transplant included age, sex, and race as reported by the transplant center.

Pharmacy fill data were assembled by linking SRTR records for kidney transplant recipients with billing claims from Symphony Health Solutions (SHS), a large US pharmaceutical claims data warehouse that collects prescription drug fill records including self-paid fills and those reimbursed by private and public payers. SHS comprises National Council for Prescription Drug Program format prescription claims aggregated from multiple sources including claims warehouses, retail pharmacies, and prescription benefit managers for approximately 60% of US retail pharmacy transactions. Individual claim records include the date of a given pharmacy fill with the National Drug Code identifying agent and dosage. After Institutional Review Board and HRSA approvals, SHS records were linked with SRTR records for kidney transplant recipients. A deterministic de-identification strategy was applied, wherein patient identifiers (last name, first name, date of birth, sex, and ZIP code of residence) were transformed before delivery to the Saint Louis University researchers with Health Information Portability and Accountability Act and HITECH-certified encryption technology from SHS. The patient de-identification software employs multiple encryption algorithms in succession to guarantee that the resulting "token" containing encrypted patient identifiers can never be decrypted. However, the algorithm yields the same results for a given set of data elements, such that linkages by unique anonymous tokens are possible.

Sampling and exposure definitions

Patients selected for the primary analysis had SRTR records of kidney transplantation, underwent transplant between January 2008 and January 2015, and had at least 1 year of available pharmaceutical fill records before transplant. Patient clinical and demographic characteristics, as well characteristics of the donated organ and other transplant factors, were defined by the OPTN Transplant Candidate and Recipient Registration forms (Table 1). The primary exposure of interest was pharmacy claims for antidepressant medications in the year before transplant, including selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, newer-generation antidepressants, and combination pills (Table S1). Medications primarily indicated for bipolar disorder, such as lithium, were not included. We also quantified the months that antidepressants were dispensed to patients in the 12-month period before transplant, among those with at least 12 months of pre-transplant pharmacy records, as a metric of the intensity of exposure [14–17]. To account for concomitant use of multiple agents, the metric for any antidepressant exposure aggregated fill days from different classes even if prescription dates were overlapping [14–17]. Separate analyses quantified antidepressant use in the year before wait-listing and in the first year after transplantation.

Death and graft failure

Mortality was defined as death from any cause. Graft failure was defined as return to maintenance dialysis or "preemptive" retransplantation. All-cause graft failure included graft loss due to patient death. Observation time for outcomes in the first year post-transplant was censored at day 365 after transplantation or study end (January 31, 2015). To assess the implications of antidepressant use in the first year of transplant, we examined clinical outcomes from >1 to 2 years post-transplant or end of study. Finally, to frame post-transplant outcomes in the context of survival on the waiting list, we examined associations of pre-listing antidepressant use with death after listing.

Statistical analyses

Datasets were merged and analyzed with SAS (Statistical Analysis Software) version 9.4 (SAS Institute Inc., Cary, NC, USA). Distributions of clinical and demographic traits among recipients with antidepressant exposure, compared with no antidepressant use, were compared by the chi-square test. Propensity models for the likelihood of any antidepressant use in the pre-transplant period and the first year post-transplant were constructed by multivariable logistic regression [10,11].

The log-rank test was used to assess the statistical significance of differences in unadjusted incidence of patient death and graft loss according to pre-transplant antidepressant use, as well as differences in these outcomes after the first transplant anniversary according to first year antidepressant use. Adjusted associations of antidepressant use with graft failure and death [adjusted hazards ratio (aHR)] were quantified by multivariable Cox regression including adjustment for recipient, donor, and transplant clinical factors as listed in Table 1. Outcome models were also stratified by quintile of propensity for antidepressant use as previously described in similar studies of medication use and post-transplant outcomes, to minimize the effect of confounding by indication [10,11]. We also examined associations of transplantation with death on the wait list among those who did and did not fill antidepressants before listing by modeling transplant as a time-varying predictor of post-listing mortality, including adjustment for baseline candidate demographic and clinical traits.

Results

Clinical correlates of antidepressant use before and after transplant

Between January 2008 and January 2015, 80 849 adult recipients of kidney-only transplants were recorded in the SRTR database. Of these, 72 054 had linked pharmacy claims 1 year before transplant. Among the eligible sample, 12.6% filled an antidepressant in the year before transplant; distribution of duration of use was <2 months, $n = 3026$; 2–5 months, $n = 3186$; and >5 months, $n = 2868$. The most common class of antidepressant filled before transplant was SSRIs (61.7%), followed by newer-generation antidepressants (25.3%) and tricyclic antidepressant therapy (12.9%); combination therapies accounted for only 0.1% of overall use.

Distributions of baseline clinical traits according to pre-transplant antidepressant use are shown in Table 1. Compared with transplant recipients who did not fill antidepressants before transplant, those who used antidepressants were more commonly aged 18–30 years, women, white, unemployed, had limited functional capacity, and were more likely to have chronic

Table 1. Distributions of clinical traits in the study sample according to pre-transplant antidepressant use level and propensity of using antidepressants before and after transplant.

	Traits by pre-transplant use		Propensity model associations	
	No use (N = 62 974) %	Some use (N = 9080) %	Pre-transplant use Adjusted odds ratio (95% CI)	Post-transplant use Adjusted odds ratio (95% CI)
Recipient factors				
Age, years		‡		
<18	5.1	2.5	0.32 (0.25–0.41)‡	0.57 (0.44–0.73)‡
18–30	7.7	10.3	Reference	Reference
31–45	19.5	21.3	0.91 (0.81–1.02)	1.04 (0.91–1.20)
46–60	36.6	38.0	0.83 (0.74–0.93)†	1.00 (0.87–1.14)
>60	31.2	27.9	0.63 (0.56–0.71)‡	0.89 (0.77–1.02)
Female	38.8	43.7‡	1.23 (1.16–1.31)‡	1.30 (1.21–1.40)‡
Race		‡		
White	52.5	61.2	1.59 (1.47–1.73)‡	1.47 (1.34–1.61)‡
Black	26.7	21.0	Reference	Reference
Hispanic	14.1	13.6	1.21 (1.09–1.34)†	1.00 (0.88–1.13)
Other	6.7	4.3	0.82 (0.70–0.96)*	0.66 (0.55–0.80)‡
Body mass index, kg/m^2		*		
<18.5	4.2	3.3	1.01 (0.84–1.21)	0.82 (0.66–1.01)
18.5–25	28.7	28.5	Reference	Reference
25–30	31.5	31.4	1.02 (0.94–1.10)	0.97 (0.89–1.06)
>30	33.2	33.9	1.00 (0.92–1.08)	1.01 (0.93–1.10)
Missing	2.5	3.0	1.23 (1.02–1.48)*	0.99 (0.81–1.22)
Cause of ESRD		‡		
Diabetes	23.4	25.8	1.10 (0.95–1.26)	1.07 (0.91–1.26)
Glomerulonephritis	23.1	25.5	1.10 (1.00–1.21)	0.98 (0.88–1.09)
Hypertension	25.5	21.8	0.92 (0.83–1.02)	0.90 (0.80–1.01)
Polycystic kidney disease	9.9	9.4	0.97 (0.86–1.10)	1.00 (0.87–1.14)
Other	18.1	17.5	Reference	Reference
ESRD duration, mos.		‡		
None (preemptive)	18.0	12.7	0.59 (0.53–0.65)‡	0.95 (0.86–1.05)
>0–24	29.3	36.7	Reference	Reference
25–60	31.1	32.4	0.82 (0.76–0.88)‡	0.96 (0.87–1.05)
>60	20.8	17.5	0.68 (0.62–0.75)‡	1.05 (0.94–1.17)
Missing	0.8	0.7	0.70 (0.50–1.00)*	1.21 (0.88–1.66)
Comorbidities				
Diabetes	32.0	34.1*	1.03 (0.92–1.15)	1.05 (0.93–1.20)
Coronary disease/angina	5.7	6.5*	1.05 (0.97–1.14)	1.00 (0.92–1.10)
COPD	1.2	1.7†	1.07 (0.89–1.29)	1.01 (0.81–1.24)
Hypertension	78.4	78.7	0.92 (0.78–1.08)	1.08 (0.90–1.29)
Cerebral vascular disease	2.3	2.7	1.32 (1.05–1.67)*	0.99 (0.72–1.35)
Peripheral vascular disease	3.4	3.7	1.09 (0.96–1.23)	1.01 (0.88–1.17)
Highest level of education		†		
College/Graduate school	47.1	45.7	Reference	Reference
High school or lower	43.7	46.3	1.09 (1.02–1.17)*	1.08 (1.00–1.16)*
Unknown	9.1	8.0	0.96 (0.85–1.08)	0.94 (0.83–1.07)
Employment status		‡		
Working	30.3	24.9	Reference	Reference
Not working	57.4	64.6	1.40 (1.29–1.51)‡	1.18 (1.08–1.28)†
Unknown	12.3	10.5	1.39 (1.23–1.57)‡	1.16 (1.01–1.33)*
Functional capacity		‡		
No Limitations	65.0	63.5	Reference	Reference
Limited	6.6	9.0	1.25 (1.12–1.39)‡	1.14 (1.01–1.30)*
Unknown	28.5	27.5	1.08 (1.00–1.16)*	0.98 (0.91–1.07)

Table 1. Continued.

	Traits by pre-transplant use		Propensity model associations	
	No use (N = 62 974) %	Some use (N = 9080) %	Pre-transplant use Adjusted odds ratio (95% CI)	Post-transplant use Adjusted odds ratio (95% CI)
Insurance type		†		
Private	36.0	33.7	Reference	Reference
Public	64.0	66.3	0.90 (0.83–0.97)*	0.98 (0.90–1.07)
Previous transplant	13.5	14.8*	Not applicable to pre-transplant use	0.87 (0.78–0.97)*
PRA level (most recent)		†		
<10	69.3	67.4		Reference
10 to 79	18.4	18.7		1.07 (0.98–1.17)
≥80	6.7	8.2		1.04 (0.90–1.20)
Missing	5.7	5.7		0.91 (0.76–1.10)
Transplant and donor factors				
HLA mismatches		*		
Zero A, B, and DR	7.8	9.2		1.03 (0.92–1.16)
Zero DR	11.3	11.3		1.02 (0.91–1.13)
Other	80.9	79.5		Reference
Donor type		*		
Living	36.0	38.4		1.03 (0.94–1.12)
Standard criteria deceased	44.6	42.9		Reference
Expanded criteria deceased	9.4	8.9		1.02 (0.90–1.16)
Donation after cardiac death	10.0	9.8		1.21 (1.07–1.36)†
Year of transplant		‡		
2007–2009	19.5	22.6	Reference	Reference
2010–2012	46.4	47.8	0.90 (0.84–0.97)*	0.74 (0.69–0.79)‡
2013–2015	34.0	29.6	0.77 (0.71–0.84)‡	0.70 (0.63–0.77)‡

P-values: *P < 0.05–0.002; †P = 0.001–0.0001; ‡P < 0.0001.

COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; HLA, human leukocyte antigen; PRA, panel reactive antibody. "Other race" includes Asian, Native American, Pacific Islander, and multiracial.

obstructive pulmonary disease (COPD). Considered in terms of any fills and adjusted for other baseline factors, pre-transplant antidepressant use was 59% more likely among white versus black patients [adjusted odds ratio (OR), 1.59, 95% CI 1.47–1.73], 23% more likely among women than among men (aOR 1.23, 95% CI 1.16–1.31), and 40% more likely among unemployed than among employed recipients (aOR 1.40, 95% CI 1.29–1.51) (Table 1). Recipients who filled antidepressants before transplant were less likely to undergo preemptive transplant, and antidepressant use declined among transplant recipients in more recent years. Similarly, the strongest correlates of antidepressant use in the year after transplant were white race (aOR 1.47, 95% CI 1.34–1.61) and female sex (aOR 1.30, 95% CI 1.21–1.40); other patterns for use in the year after transplant were similar but attenuated compared with associations with pre-transplant antidepressant use (Table 1).

Patient and graft survival according to antidepressant medication use

Over the first year post-transplant, unadjusted patient death was higher for recipients who used antidepressants in the year before transplant than for those who did not (3.5% vs. 2.5%; P < 0.0001) (Fig. 1). After multivariate adjustment for recipient, donor, and transplant factors, and for propensity for the likelihood of pre-transplant antidepressant fills (Table 1), recipients who filled antidepressants in the year before transplant had 39% higher risk of death (aHR 1.39, 95% CI 1.18–1.64) over the first year than nonusers (Fig. 2; Table S2). Pre-transplant antidepressant use was also independently associated with increased risk of all-cause graft loss (aHR 1.15, 95% CI 1.02–1.30), although the association was driven by death, and antidepressant medication use before transplant was not associated with death-censored graft failure over the first year (aHR 0.97, 95% CI

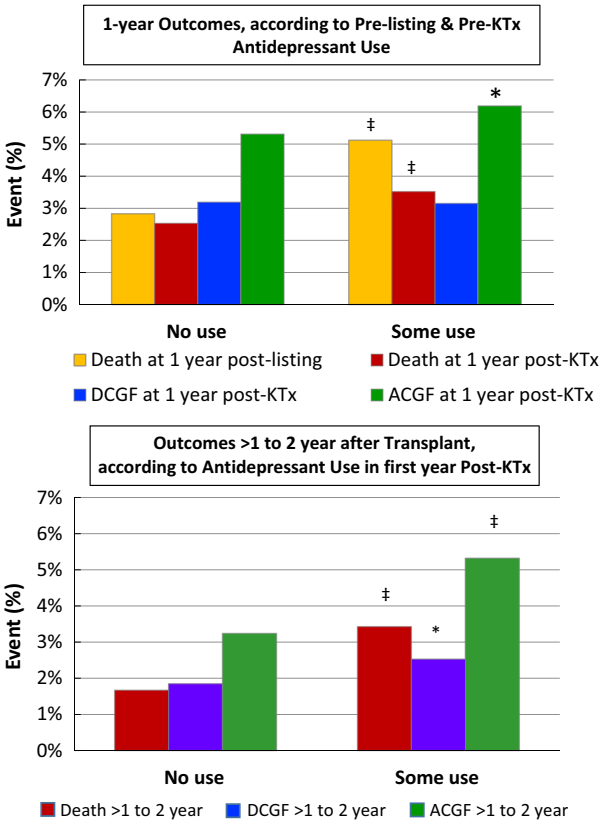

Figure 1 Death and graft failure according to antidepressant use before and after kidney transplant. *P*-values: *$P < 0.05$–0.002; †$P = 0.001$–0.0001; ‡$P < 0.0001$, for differences in 1-year outcomes in those who filled antidepressants compared with no use. ACGF, all-cause graft failure; DCGF, death-censored graft failure; KTx, kidney transplant.

0.82–1.15). Outcomes did not differ according to class of antidepressant medication, or with duration of pre-transplant fills.

Patient death (3.4% vs. 1.7%; $P < 0.0001$), death-censored graft failure (2.5% vs. 1.9%; $P = 0.0006$), and all-cause graft loss (5.3% vs. 3.2%; $P < 0.0001$) from >1 to 2 years post-transplant were all higher among patients who filled antidepressants in the year after transplant than for nonusers (Fig. 1). After multivariate and propensity adjustment, antidepressant use in the first year after transplant was associated with nearly twice the risk of death (aHR 1.94, 95% CI 1.60–2.35), 36% higher death-censored graft failure risk (aHR 1.36, 1.08–1.70), and 61% higher all-cause graft failure risk (aHR 1.60, 95% CI 1.37–1.88) in the subsequent year (Fig. 2; Table S3).

Among candidates with 1 year of pre-listing pharmacy fill records, 12% filled antidepressants in the year before listing. Similar to the associations of antidepressant use with post-transplant death risk, compared with those who did not fill antidepressants, patients who used antidepressants in the year before listing had higher rates of 1-year transplant-censored mortality (aHR 1.65, 95% CI 1.48–1.76). Importantly, transplantation was associated with approximately 60% reductions in the risk death after listing among patients who filled antidepressants before listing (aHR 0.42, 95% CI 0.38–0.46), similar to the effect among those without pre-listing antidepressant medication fills (aHR 0.43, 95% CI 0.41–0.45). We did not observe interactions between antidepressant use and baseline factors on study outcomes.

Antidepressant use patterns before and after transplant

To assess the persistence of pre-transplant antidepressant use patterns post-transplant, we examined a subgroup of recipients with pharmacy database activity extending from 1 year pre-transplant to 1 year post-transplant ($n = 64\,453$). Overall, 51.8% of patients who filled an antidepressant medication pre-transplant continued to use post-transplant, while 13.2% of patients with no history of antidepressant medication use initiated antidepressant therapy in the first year post-transplant.

A graded pattern of post-transplant antidepressant use was noted based on the duration of pre-transplant use. Recipients with more than 5 months of pre-transplant antidepressant use continued to use antidepressants post-transplant; 58.4% filled for more than 5 months and only 20.9% did not fill antidepressants in this period (Fig. 3). In contrast, only 7.3% of recipients who did not use antidepressants pre-transplant filled for more than 5 months in the first year post-transplant; 2.5% filled for 2–5 months and 3.4% for less than 2 months. Clinical correlates of new antidepressant initiation after transplant included factors associated with pre-transplant use such as female sex, white race, diabetes, COPD, lower education level, unemployment, and limited functional status. Additional factors associated with new initiation of antidepressant therapy after transplant included obesity, coronary artery disease, cerebrovascular disease, previous transplant, and, in contrast to any pre-transplant use, more recent year of transplant (Table S4).

Discussion

We examined a linkage of national transplant registry data with outpatient prescription fill records from a

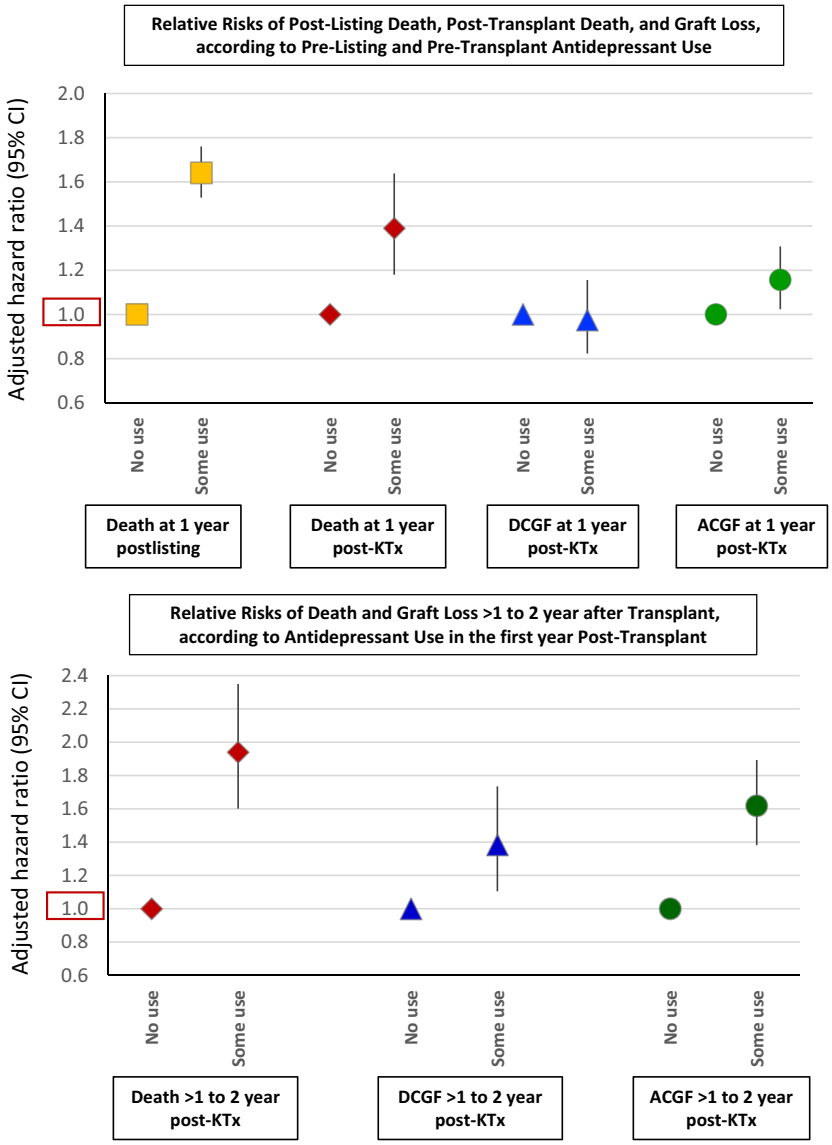

Figure 2 Adjusted associations of antidepressant use before and after kidney transplant with subsequent death and graft failure. Adjusted for recipient, donor, and transplant clinical factors as listed in Table 1 (Table S3). ACGF, all-cause graft failure; DCGF, death-censored graft failure; KTx, kidney transplant.

pharmaceutical claims warehouse to examine the use of antidepressant medications before and after kidney transplantation, and observed several key findings. (i) Overall, 12.6% of recipients filled antidepressant medications in the year before transplant, and use was more common among recipients who were women, white, unemployed, and those with limited functional status. (ii) More than 50% of patients who filled antidepressants pre-transplant continued to use after transplant, and continued use was more common among those with more sustained pre-transplant antidepressant use. (iii) Thirteen percent of recipients who did not use antidepressants before transplant initiated treatment in the first year after transplant. Correlates of new antidepressant initiation also included obesity, coronary artery disease, cerebrovascular disease, and previous transplantation. (iv) Pre-transplant antidepressant use was associated with 40% higher adjusted mortality risk and 20% higher all-cause graft loss risk in the first year after transplant. (v) Antidepressant use in the first year after transplantation had important prognostic implications, predicting twice the risk of death, 38% higher death-censored graft failure risk, and 61% higher all-cause graft loss risk over the next year compared with no use. (vi) Pre-listing antidepressant use was also associated with increased mortality compared with no use, but transplantation conferred a survival benefit regardless of pre-listing antidepressant use status.

Prior studies have examined the prevalence of depression among samples of transplant recipients defined by self-reported symptoms using assessment scales such as the Beck Depression Inventory, the

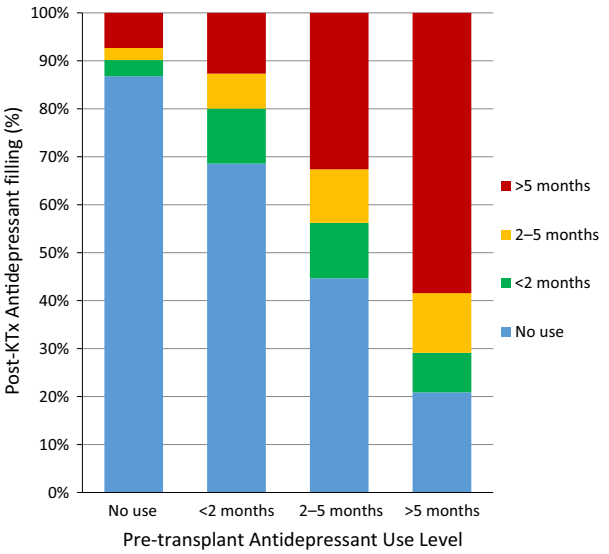

Figure 3 Post-transplant antidepressant filling patterns according to pre-transplant antidepressant use. KTx, kidney transplant.

Hospital Anxiety and Depression Scale (HADS), the Center for Epidemiologic Studies Depression Scale (CES-D), the Zung Self Rating Depression Scale, and the Taiwanese Depression Questionnaire [4,5,9,18–22]. These studies differ in sampling and design and were performed in diverse locations including Turkey, Iran, Hungary, Taiwan, Japan, the Netherlands, and the United Kingdom as well as the United States. A recent meta-analysis of studies from 2004 to 2015 (four cross-sectional and two case–control) found that depression symptoms among transplant recipients ranged from 14.8% to 41%, but rates were consistently lower than in dialysis patients [23]. Our design differs in examining medication-treated depression, a measure that requires a patient to report symptoms to a care provider and accept pharmacotherapy. Dobbels *et al.* [7] used billing claims, a study measure that also requires patients to come to clinical attention for depressive symptoms, to identify depression in Medicare-insured US kidney transplant recipients (1995–2003), and identified depression diagnoses in 5% by 1 year post-transplant. Administrative data including pharmacy fill records offer an additional perspective on transplant-related mental health outcomes diagnosed in real practice that can complement and extend observations obtained through surveys, interviews, and case reports in smaller samples. In interpreting our results, however, it is important to note that antidepressant medications may be used for other conditions including anxiety, obsessive–compulsive disorders and neuropathic pain, or off-label uses.

Consistent with prior studies [7], we found that female transplant recipients more commonly received pharmacotherapy for depression than male recipients. Gender-based variation in the frequency of reported depression is well established in the general population. For example, a nationally representative face-to-face household survey in 48 states estimated that the lifetime odds of depression for American women are 1.7 times the odds for men (95% CI 1.5–2.0) [24]. We previously observed that depression diagnoses were more than twice as common in female than in male living kidney donors and that this pattern was consistent among nondonor beneficiaries in the same insurance plan [25]. In the current study, women were more likely to fill antidepressant medications before transplant and in the year after transplant, and were 70% more likely than men to start new antidepressant therapy after transplant.

We also found that white recipients were more likely to fill antidepressant medications before transplant and after transplant, and were more than twice as likely as African Americans to start new antidepressant therapy after transplant. Significantly lower lifetime prevalence of major depressive disorder was identified among African Americans (aOR 0.51) and Hispanics (aOR 0.38) compared with white participants in the National Health and Nutrition Examination Survey (NHANES) III [26]. The mechanism of lower frequencies of clinically detected depression among persons of nonwhite race and ethnic backgrounds appears to be in part due to reluctance of members of minority groups to seek mental health care and indirect, or "culture bound." presentations. An investigation of the symptomatology of depressed Chinese Americans found that 42% of those with major depression initially presented with physical complaints, while none reported complaints of mood alteration [27]. Manifestation of depression with somatic, rather than mental or emotional symptoms has been identified in Hispanic and Asian Indian populations [28,29]. Reduced access to adequate treatment for acute depression, defined by specialty provider encounters and use of antidepressant therapy, has been reported among African Americans and Asians with depression [30]. Notably, transplant recipients receive disease-specific Medicare entitlement for the first 3 years post-transplant and have regular follow-up visits under monitoring protocols, supporting that access barriers are not the primary determinant of racial differences in depression care after transplant. Future research should investigate whether demographic differences in measures of depression, including use of antidepressant medications, reflect care seeking, clinical ascertainment, or true differences in disease burden.

We also found that use of antidepressant therapy before transplant was independently associated with increased risk of death and graft loss in the first year after transplant and that recipients who filled antidepressants in the first year after transplant had nearly twice the risk of subsequent death and 38% higher death-censored graft failure risk compared with those who did not require antidepressants. These observations are consistent with a study of 527 kidney transplant recipients in the Netherlands that identified associations of depression defined by a symptom checklist with twice the risk of cardiovascular and all-cause mortality over an average of 7 years of follow-up [9]. Similarly, in a cohort of 840 kidney transplant recipients in Hungary, mortality was higher among those with versus without depressive symptoms defined by the CES-D scale (21% vs. 13% over a mean 58 months follow-up) [8]. Symptoms of depression may be a manifestation of underlying medical conditions, and depression has been implicated as a risk factor for mortality among patients with a variety of chronic health conditions including heart failure [31], coronary artery disease [32], rheumatoid arthritis [33], lupus [34], COPD [35], and diabetes [36], among others. While the association of depression with mortality may reflect confounding from other comorbid conditions, various causal mechanisms have also been proposed. Patients who are depressed may have increased nonadherence [37,38], less physical activity, poor eating habits, or substance use behaviors including smoking and alcohol use [39]. Other proposed bio-behavioral mechanisms include autonomic dysregulation [40], increased platelet aggregation [41], underlying inflammation [42], and even reduced cellular immunity [43]. For transplant recipients, compliance with medical care is of particular concern and includes the need to adhere to immunosuppression therapy and other transplant-related medications, perform regular laboratory testing, and attend follow-up appointments [44,45]. Nonadherence among transplant recipients is often difficult to diagnose, but when recognized, has been shown to correlate strongly with preventable allograft loss and poor patient outcomes [46,47]. Future studies should examine possible connections between measures of depression including pharmacological treatment, care adherence, other behaviors including substance use, and outcomes among transplant recipients.

Regardless of the mechanisms of association, identification of novel markers of post-transplant outcomes is timely and can help transplant programs assess and manage risk at a programmatic level. Transplantation in the USA is an increasingly regulated field with a high level of public reporting. Transplant centers are graded for recipient and graft survival using risk-adjusted equations developed by SRTR to predict expected 1- and 3-year post-transplant patient and graft survival [48]. Importantly, SRTR equations do not adjust for mental health conditions or medication use history as risk factors for post-transplant death or graft loss. Thus, centers performing transplants in patients who require antidepressant therapies before and after transplant should be aware of additional risk that will not be recognized by SRTR, and should consider extra monitoring and focused post-transplant care of these recipients.

Our study has limitations. Observational designs can determine associations but cannot prove causation. The available data do not include detailed clinical information that may explain indications for or contraindications to antidepressant medications or describe mental health or adherence behaviors. Importantly, antidepressant medications may be used for other conditions including anxiety, obsessive–compulsive disorders and neuropathic pain, or given off-label to treat eating disorders, Tourette syndrome, and fibromyalgia. Antidepressant medication use is also affected by patient willingness to seek care and report symptoms [26,28,29], and prescription records do not offer severity information that can be obtained through surveys and interviews [49]. Our study sample was limited to patients who passed a transplant evaluation and were deemed suitable to undergo transplant, and the severity and outcome implications of depression likely differ in the broader population of patients with end-stage renal disease. Future projects linking the transplant registry and pharmacy fill records with electronic medical records or surveys may be useful in defining relationships of antidepressant use, depression symptoms, and outcomes among transplant candidates and recipients. Antidepressant use in the current study was defined in the years before and after transplant, and in the year before listing; additional studies should examine the impact of antidepressant fills over other time windows.

In conclusion, based on integration of pharmacy fill records with transplant registry data for a national US sample, we found that use of antidepressant medications before and after kidney transplant is more common among women, recipients of white race, and those with functional limitations, and has prognostic implications for patient and allograft survival. Importantly, while pre-listing antidepressant use was also associated with increased mortality compared with no use, transplantation conferred a survival benefit regardless of pre-listing antidepressant use status. Although the study design and available data are inherently affected by patient–provider communication, these data offer an additional

perspective on treated mental health conditions among transplant recipients that complements information obtained through surveys and interviews. Further work including granular measures of patient behavior, adherence to transplant-related care regimens, and possible bio-behavioral pathways is needed to define the mechanisms of these associations. For now, these data suggest that transplant candidates and recipients who require antidepressant therapy warrant careful evaluation and management, perhaps by a multidisciplinary team including sustained social worker, psychologist and/or psychiatrist support, as well as focused monitoring of clinical status after transplantation.

Authorship

KLL, GPH and MAS: participated in study design, acquisition of data and regulatory approvals, data analysis and writing of the manuscript. ASN, RO, HR, RG, NNL, GPH and BLK: participated in study design, interpretation and writing of the manuscript. ZZ: participated in data analysis and manuscript preparation. DAA, DLS, VRD and DCB: participated in study design, interpretation and writing of the manuscript.

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Conflicts of interest

The authors have declared no conflicts of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article:

Table S1. Antidepressant medications included in the definition of pharmacologically treated depression.

Table S2. Adjusted associations of pre-transplant antidepressant use with risks of death and graft loss over 1 year after kidney transplant.

Table S3. Adjusted associations of antidepressant use in the first year post-transplant with risks of death and graft loss >1 to 2 yr after transplant.

Table S4. Adjusted associations of baseline factors with new initiation of antidepressant medication after kidney transplantation.

REFERENCES

1. Dew MA, Switzer GE, DiMartini AF, Matukaitis J, Fitzgerald MG, Kormos RL. Psychosocial assessments and outcomes in organ transplantation. *Prog Transplant* 2000; **10**: 239; quiz 60.
2. Strine TW, Mokdad AH, Balluz LS, *et al.* Depression and anxiety in the United States: findings from the 2006 behavioral risk factor surveillance system. *Psychiatr Serv* 2008; **59**: 1383.
3. Schnitzler MA, Whiting JF, Brennan DC, *et al.* The life-years saved by a deceased organ donor. *Am J Transplant* 2005; **5**: 2289.
4. Akman B, Özdemir F, Sezer S, Miçozkadioğlu H, Haberal M, eds. Depression levels before and after renal transplantation. *Transpl Proc* 2004; **36**: 111.
5. Szeifert L, Molnar MZ, Ambrus C, *et al.* Symptoms of depression in kidney transplant recipients: a cross-sectional study. *Am J Kidney Dis* 2010; **55**: 132.
6. Tsunoda T, Yamashita R, Kojima Y, Takahara S, eds. Risk factors for

depression after kidney transplantation. *Transpl Proc* 2010; **42**: 1679.
7. Dobbels F, Skeans MA, Snyder JJ, Tuomari AV, Maclean JR, Kasiske BL. Depressive disorder in renal transplantation: an analysis of Medicare claims. *Am J Kidney Dis* 2008; **51**: 819.
8. Novak M, Molnar MZ, Szeifert L, *et al.* Depressive symptoms and mortality in patients after kidney transplantation: a prospective prevalent cohort study. *Psychosom Med* 2010; **72**: 527.
9. Zelle DM, Dorland HF, Rosmalen JG, *et al.* Impact of depression on long-term outcome after renal transplantation: a prospective cohort study. *Transplantation* 2012; **94**: 1033.
10. Lentine KL, Yuan H, Tuttle-Newhall JE, *et al.* Quantifying prognostic impact of prescription opioid use before kidney transplantation through linked registry and pharmaceutical claims data. *Transplantation* 2015; **99**: 187.
11. Lentine KL, Lam NN, Xiao H, *et al.* Associations of pre-transplant prescription narcotic use with clinical complications after kidney transplantation. *Am J Nephrol* 2015; **41**: 165.
12. Alhamad T, Brennan DC, Brifkani Z, *et al.* Pretransplant midodrine use: a newly identified risk marker for complications after kidney transplantation. *Transplantation* 2016; **100**: 1086.
13. Williams JM, Tuttle-Newhall JE, Schnitzler M, *et al.* Clopidogrel use as a risk factor for poor outcomes after kidney transplantation. *Am J Surg* 2014; **208**: 556.
14. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med* 2005; **353**: 487.
15. Lentine KL, Villines TC, Xiao H, *et al.* Cardioprotective medication use after acute myocardial infarction in kidney transplant recipients. *Transplantation* 2011; **91**: 1120.
16. Lentine KL, Schnitzler MA, Garg AX, *et al.* Understanding antihypertensive medication use after living kidney donation through linked national registry and pharmacy claims data. *Am J Nephrol* 2014; **40**: 174.
17. Lentine KL, Lam NN, Schnitzler MA, *et al.* Gender differences in use of prescription narcotic medications among living kidney donors. *Clin Transplant* 2015; **29**: 927.
18. Karaminia R, Tavallaii SA, Lorgard-Dezfuli-Nejad M, *et al.* Anxiety and depression: a comparison between renal transplant recipients and hemodialysis patients. *Transplant Proc* 2007; **39**: 1082.
19. Alavi N, Aliakbarzadeh Z, Sharifi K, eds. Depression, anxiety, activities of daily living, and quality of life scores in patients undergoing renal replacement therapies. *Transpl Proc* 2009; **41**: 3693.
20. Spencer BW, Chilcot J, Farrington K. Still sad after successful renal transplantation: are we failing to recognise depression? An audit of depression screening in renal graft recipients. *Nephron Clin Pract* 2011; **117**: c106.
21. Lin YH, Yang Y, Chen SY, Chang CC, Chiu PF, Huang CY. The depression status of patients with end-stage renal disease in different renal replacement therapies. *Int J Urol Nurs* 2011; **5**: 14.
22. Troen AM, Scott TM, D'Anci KE, *et al.* Cognitive dysfunction and depression in adult kidney transplant recipients: baseline findings from the FAVORIT Ancillary Cognitive Trial (FACT). *J Ren Nutr* 2012; **22**: 268.
23. Veater NL, East L. Exploring depression amongst kidney transplant recipients: a literature review. *J Ren Care* 2016; **42**: 172.
24. Kessler RC, Berglund P, Demler O, *et al.* The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA* 2003; **289**: 3095.
25. Lentine KL, Schnitzler MA, Xiao H, *et al.* Depression diagnoses after living kidney donation: linking U.S. Registry data and administrative claims. *Transplantation* 2012; **94**: 77.
26. Riolo SA, Nguyen TA, Greden JF, King CA. Prevalence of depression by race/ethnicity: findings from the National Health and Nutrition Examination Survey III. *Am J Public Health* 2005; **95**: 998.
27. Yeung A, Chan R, Mischoulon D, *et al.* Prevalence of major depressive disorder among Chinese-Americans in primary care. *Gen Hosp Psychiatry* 2004; **26**: 24.
28. Raguram R, Weiss MG, Channabasavanna SM, Devins GM. Stigma, depression, and somatization in South India. *Am J Psychiatry* 1996; **153**: 1043.
29. Mischoulon D. Psychiatric management of Hispanic patients: cross-cultural issues and ethnopsychopharmacology. Program and Abstracts of the American Psychiatric Association 2004 Annual Meeting. 2004: Symposium 75C.
30. Alegria M, Chatterji P, Wells K, *et al.* Disparity in depression treatment among racial and ethnic minority populations in the United States. *Psychiatr Serv* 2008; **59**: 1264.
31. Freedland KE, Hesseler MJ, Carney RM, *et al.* Major depression and long-term survival of patients with heart failure. *Psychosom Med* 2016; **78**: 896.
32. Barth J, Schumacher M, Herrmann-Lingen C. Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis. *Psychosom Med* 2004; **66**: 802.
33. Ang DC, Choi H, Kroenke K, Wolfe F. Comorbid depression is an independent risk factor for mortality in patients with rheumatoid arthritis. *J Rheumatol* 2005; **32**: 1013.
34. Palagini L, Mosca M, Tani C, Gemignani A, Mauri M, Bombardieri S. Depression and systemic lupus erythematosus: a systematic review. *Lupus* 2013; **22**: 409.
35. Ng T-P, Niti M, Tan W-C, Cao Z, Ong K-C, Eng P. Depressive symptoms and chronic obstructive pulmonary disease: effect on mortality, hospital readmission, symptom burden, functional status, and quality of life. *Arch Intern Med* 2007; **167**: 60.
36. Katon WJ, Rutter C, Simon G, *et al.* The association of comorbid depression with mortality in patients with type 2 diabetes. *Diabetes Care* 2005; **28**: 2668.
37. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. *Arch Intern Med* 2000; **160**: 2101.
38. Cukor D, Rosenthal DS, Jindal RM, Brown CD, Kimmel PL. Depression is an important contributor to low medication adherence in hemodialyzed patients and transplant recipients. *Kidney Int* 2009; **75**: 1223.
39. Mikolajczyk RT, El Ansari W, Maxwell AE. Food consumption frequency and perceived stress and depressive symptoms among students in three European countries. *Nutr J* 2009; **8**: 1.
40. Kinder LS, Kamarck TW, Baum A, Orchard TJ. Depressive symptomatology and coronary heart disease in Type I diabetes mellitus: a study of possible mechanisms. *Health Psychol* 2002; **21**: 542.
41. Lederbogen F, Gilles M, Maras A, *et al.* Increased platelet aggregability in major depression? *Psychiatry Res* 2001; **102**: 255.
42. Penninx BW, Kritchevsky SB, Yaffe K, *et al.* Inflammatory markers and depressed mood in older persons: results from the Health, Aging and Body Composition study. *Biol Psychiat* 2003; **54**: 566.
43. Fortes C, Farchi S, Forastiere F, *et al.* Depressive symptoms lead to impaired cellular immune response. *Psychother Psychosom* 2003; **72**: 253.
44. Williams AF, Manias E, Gaskin CJ, Crawford K. Medicine non-adherence in kidney transplantation. *J Ren Care* 2014; **40**: 107.
45. Denhaerynck K, Steiger J, Bock A, *et al.* Prevalence and risk factors of non-

adherence with immunosuppressive medication in kidney transplant patients. *Am J Transplant* 2007; **7**: 108.
46. De Geest S, Borgermans L, Gemoets H, *et al.* Incidence, determinants, and consequences of subclinical noncompliance with immunosuppressive therapy in renal transplant recipients. *Transplantation* 1995; **59**: 340.
47. Vlaminck H, Maes B, Evers G, *et al.* Prospective study on late consequences of subclinical non-compliance with immunosuppressive therapy in renal transplant patients. *Am J Transplant* 2004; **4**: 1509.
48. Scientific Registry of Transplant Recipients (SRTR). Risk Adjustment Models. Available at: http://www.srtr.org/csr/current/modtabs.aspx. Accessed: February 7, 2017.
49. Melfi CA, Croghan TW. Use of claims data for research on treatment and outcomes of depression care. *Med Care* 1999; **4**(Suppl Lilly): AS77.