

Research Paper

# Evaluating the utilisation and expenditure patterns of erythropoietin stimulating agents and immunosuppressants in Australian chronic kidney disease patients

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## Abstract

**Objectives** This study aimed to characterise utilisation and expenditure patterns associated with erythropoietin stimulating agents (ESAs) (darbepoetin alfa, epoetin alfa, epoetin beta, epoetin lambda and methoxy polyethylene glycol-epoetin beta) and immunosuppressants (mycophenolate, tacrolimus, ciclosporine, sirolimus and everolimus) in the Australian chronic kidney disease (CKD) population from 2010–2018.

**Methods** Utilisation and expenditure data for each drug were obtained from the Pharmaceutical Benefit Scheme and Highly Specialised Drugs program. Utilisation data were provided a number of dispensing per year, which was then converted to the daily defined dose per 1000 population per day for each year. Temporal trends were then analysed.

**Key findings** Over the study period, utilisation of methoxy polyethylene glycol-epoetin beta and epoetin lambda rose by 13.7 and 81.4-fold, respectively. Contrastingly, the utilisation of darbepoetin alfa, epoetin alfa and epoetin beta declined by 6%, 42% and 70%, respectively. In 2018, tacrolimus, sirolimus, everolimus and mycophenolate utilisation was up 126%, 16.9%, 125% and 182% respectively; conversely, ciclosporine utilisation dropped 19%. Total Australian expenditure on all ESAs examined remained stable at around AUD 128 million over the study period, while total Australian expenditure across all immunosuppressants increased 1.1-fold reaching just over AUD 98 million.

**Conclusions** It appears that immunosuppressant utilisation and expenditure are rising as transplantation rates in Australia continue to increase. Conversely, ESA utilisation and expenditure remained relatively unchanged over the study period. This may be due to increasing concerns around the safety of ESAs offsetting the increasing number of people with CKD.

**Keywords:** chronic kidney disease; erythropoietin stimulating agents; expenditure; immunosuppressants; utilisation

## Introduction

The prevalence of chronic kidney disease (CKD) is increasing worldwide with an estimated 1.7 million people showing signs of CKD in Australia.<sup>[1]</sup> With increasing prevalence, comes increasing costs; Kidney Health Australia estimates the cumulative costs of treating end-stage renal disease will be near AUD12 billion from 2009–2020.<sup>[2]</sup> Pharmaceuticals contribute to a large portion of these costs; two major classes of medications used in this population are erythropoietin stimulating agents (ESAs) and immunosuppressants, both of which are expensive.

Anaemia is a relatively common comorbidity for CKD patients, having been shown to effect up to 50% of people with stage five kidney disease.<sup>[3]</sup> It increases in prevalence and severity as a patient's kidney function and glomerular filtration rate decline.<sup>[4, 5]</sup> Although multifactorial, its primary cause is the inability of the kidneys to produce sufficient erythropoietin to support erythropoiesis.<sup>[6]</sup> Transplantation is a major risk factor for anaemia, heightened by the use of immunosuppressants.<sup>[7, 8]</sup> If left untreated anaemia is associated with a reduced quality of life and an increase in mortality and hospitalisation risk.<sup>[9]</sup> ESAs are manmade recombinant glycoproteins designed to substitute erythropoietin and stimulate red blood cell production. ESAs can be categorised as fast-acting agents administered weekly (epoetin alfa (EPOA), epoetin beta (EPOB) and epoetin lambda (EPOL)) or long-acting agents which may be dosed monthly (darbepoetin alfa (DARB) and methoxy polyethylene glycol-epoetin beta (MPEG)).

Renal transplantation is the preferred renal replacement therapy for those with end-stage CKD, given its excellent prognosis, quality of life improvements and the overall increase in survival rates.<sup>[10]</sup> However, transplant recipients must continuously take a combination of immunosuppressant agents to minimise their risk of transplant rejection. Long-term maintenance immunosuppressants such as calcineurin inhibitors (cyclosporin, tacrolimus), mTOR inhibitors (everolimus, sirolimus), antiproliferative agents (mycophenolate) and steroids are key to ensuring optimal patient outcomes.<sup>[11]</sup>

In Australia the cost of medications for patients is largely subsidised via the Pharmaceutical Benefits Scheme (PBS) and its associated programs such as the Highly Specialised Drugs (HSD) program; the latter covering medicines supplied through public and private hospitals.<sup>[12]</sup> Under these schemes, patients contribute a pre-specified co-payment before the Australian government subsidises the remaining cost of prescriptions dispensed. ESAs are currently subsidised exclusively through the HSD program, while immunosuppressants are subsidised through both the PBS and HSD schedule.

Drug utilisation research aims to assess the rational use of medicines. By optimising medicine use, we can ensure patients are receiving ideal treatment, while also managing costs to the community. The daily defined dose (DDD) system was developed for conducting drug utilisation studies and has been endorsed by the World Health Organisation. A drug's DDD represents its daily maintenance dose for its main indication.<sup>[13]</sup> This system is particularly useful for making international utilisation comparisons.

In the CKD population, there are currently no Australian studies on utilisation and expenditure patterns associated with the prescribing of ESAs. When considering the utilisation and expenditure of immunosuppressants, there are a limited number of studies none of which are considered up-to-date.<sup>[14, 15]</sup> The aim of this study was therefore to characterise utilisation and expenditure patterns of ESAs and immunosuppressants through pharmaceutical benefits schemes in the Australian CKD population from 2010 to 2018.

## Methods

### Data source

The PBS indexes drugs with unique identification codes for each strength, formulation, indication and subsidy type available.<sup>[16]</sup> Identification codes were obtained for methoxy polyethylene glycol-epoetin beta, darbepoetin alpha, epoetin alpha, epoetin beta and epoetin lambda as well as mycophenolate, ciclosporin, sirolimus, everolimus and tacrolimus (Supplementary Appendix 1). Data selectively on the use of ESA in anaemia associated with intrinsic renal disease was extracted. Data relating to all forms of transplantations were gathered for analysis as it was not always possible to obtain data exclusively related to renal transplantation.

To obtain dispensing records for scheduled items, the relevant codes were entered into the Medicare Item Statistics database.<sup>[17]</sup> The utilisation reports were generated documenting the number of PBS prescriptions dispensed and expenditure on each drug from 2010 to 2018. The utilisation from public and private hospitals was sourced from Highly Specialised Drugs (HSD) reports.<sup>[18]</sup> Although HSD data for the first half of 2014 were not available, to substitute, data from the end of 2014 and 2013 were averaged.

During the study period, there were changes to the schedule of mycophenolate. At all time points before May 2015, each entry for enteric-coated mycophenolate sodium had two independent codes. One code was for transplantation while the other code was for lupus nephritis. As of May 2015, however, these codes were combined under a new unrestricted benefit resulting in a singular code to characterise all usage. Therefore, from January 2010 to May 2015 only the codes for transplantation were used whereas following May 2015 the general code was used instead.

Data on the Australian population were sourced from the Australian Bureau of Statistics.<sup>[19]</sup> Additional data on the number of kidney, liver, heart and lung transplants performed per year were obtained for analysis.

### Data analysis

The utilisation for each drug was estimated based on the number of prescriptions subsidised by the PBS per year and the number of packs subsidised by the HSD program per quarter. From this, total milligrams or units dispensed per year were calculated for each drug. This was then converted to the daily defined dose per 1000 population per day (DDD/1000 population per day). This was done by dividing the total amount dispensed by the DDD multiplied by the population multiplied by the number of days in the year and multiplying the result by 1000. To calculate the total utilisation of each drug for each year, HSD and PBS results were then summed.

$$\frac{\text{total amount dispensed}}{\text{DDD} * \text{population} * \text{days in the year}} * 1000$$

The DDD's used were: tacrolimus 5 mg, ciclosporin 250 mg, sirolimus 3 mg, everolimus 1.5 mg, mycophenolate mofetil 2000 mg, darbepoetin alfa 4.5 mcg, MPEG 4 mcg and EPO 1000 units for all forms.<sup>[20]</sup> Mycophenolate is available in two salt forms, enteric-coated mycophenolate sodium and mycophenolate mofetil, with the active form being mycophenolic acid. The DDD was provided as the mofetil salt, to enable aggregation of all different salt forms as mycophenolic acid this was multiplied by 0.739 yielding a DDD for mycophenolic acid of 1478 mg. Formulations as the mofetil salt were adjusted to give the weight as the acid form.

Expenditure data were analysed similarly, with public expenditure being sourced from Medicare Australia and hospital

expenditure being obtained from HSD reports. The results were then summed to determine the total expenditure for each year.

Sensitivity analysis was performed to account for the change in PBS codes for enteric-coated mycophenolate formulations. Codes 2150E and 2193K which were restricted for lupus before the code changes in 2014 were included in the analysis to see the impact of this.

For immunosuppressants, additional analysis was performed on 2018 data to exclude the number of liver, heart and lung transplants performed each year. Mycophenolate and everolimus may be used for renal and cardiac allograft rejection, tacrolimus and ciclosporin for all forms of transplantation and sirolimus for only renal transplantation.<sup>[16]</sup> The ratio of heart to renal transplants was calculated and subtracted from the utilisation and expenditure of mycophenolate and everolimus and the ratio of all forms of transplantation to renal was calculated and then subtracted from the utilisation and expenditure of tacrolimus and ciclosporin.

All data were analysed using Microsoft Excel. Ethics approval was not required as the data were publicly available and de-identified.

## Results

Australian utilisation of methoxy polyethylene glycol-epoetin beta, darbepoetin alpha, epoetin alpha, epoetin beta and epoetin lambda from 2010 to 2018 is displayed in [Figure 1\(a\)](#). The DDD/1000 population per day for MPEG increased 13.7-fold from 0.01449 in 2010 to 0.19818 in 2018. From market inception, the utilisation of EPO-L rose to a height of 0.0686 DDD/1000 population per day in 2015. Following this, utilisation gradually declined to 0.04079 DDD/1000 population per day in 2018. The utilisation of all other ESAs decreased over the study period. DARB decreased by 6.4%, EPO-A decreased by 42.0% and EPO-B decreased by 70.2% over the study period. When looking at the combined utilisation of all ESAs there was only a 3.95% increase over the 9 years.

[Figure 1\(b\)](#) depicts the change in expenditure on ESAs. Overall there was little change in expenditure on these agents, from AUD 128 776 737 in 2010 to AUD 127 635 032 in 2018. For specific agents, MPEG increased from AUD 2 618 302 to AUD 35 654 813. EPO-L expenditure rose to a height of AUD 9 679 538 in 2015, before decreasing to AUD 5 686 989 in 2018. Expenditure on all other ESAs decreased over the study period. DARB dropped 17.6% from AUD 82 769 778 to AUD 68 150 106, EPO-A dropped 48.4% from AUD 27 760 682 to AUD 14 320 960 and EPO-B dropped 75.5% from AUD 15 627 975 to AUD 3 822 161.

The total utilisation of mycophenolate, ciclosporin, sirolimus, everolimus and tacrolimus over the study period is depicted in [Figure 2\(a\)](#). The largest increase in utilisation was for mycophenolate, which rose from 0.2149 to 0.60599 DDD/1000 population per day, a 182% increase. Tacrolimus increased from 0.18078 to 0.40778 DDD/1000 population per day, a 126% increase. Everolimus similarly increased from 0.0317 DDD/1000 population per day in 2010 to 0.0714 DDD/1000 population per day in 2018, a 125% increase. Sirolimus had an overall increase of 16.9%, from 0.0199 to 0.02326 DDD/1000 population per day. In contrast to all other immunosuppressants, ciclosporin utilisation declined from 0.1614 to 0.13047 DDD/1000 population per day, a 19% decrease.

When examining specific formulations of mycophenolate, in 2010 the enteric-coated form only accounted for 13% of total mycophenolate consumption. This number gradually increased and remained at around 22% of total utilisation over the final three years studied. Sensitivity analysis demonstrated that the use

of enteric-coated mycophenolate for lupus nephritis before the code change in 2015, accounted for only 1% of total mycophenolate utilisation.

Over the period studied, total government expenditure on all immunosuppressants increased 13% from AUD 86 667 235 to AUD 98 104 737. Expenditure changes for each agent are displayed in [Figure 2\(b\)](#). About each agent, everolimus had the largest increase in its expenditure from AUD 6 447 623 to AUD 14 491 490 a 125% increase over the eight years. Tacrolimus expenditure increased 41.9%, from AUD 29 861 631 to AUD 42 371 356. Sirolimus expenditure increased 25%, from AUD 3 614 909 to AUD 4 529 808. Ciclosporin expenditure dropped from AUD 20 086 483 to AUD 14 178 358, a 29% decline. Mycophenolate expenditure dropped by 16% from AUD 26 656 589 to AUD 22 533 724.

As depicted in [Figure 3](#), the number of renal transplants being performed per year has been gradually increasing, from 846 in 2010 to 1109 in 2017. At all time points observed there were significantly more renal transplants being performed than any other organ, in 2018 there were 369<sup>[21]</sup> liver, 243 lung and, 141 heart transplants<sup>[22]</sup> accounting for 40% of total organ transplants while kidney made up the other 60%. Sensitivity analysis removing potential expenditure on immunosuppressants for other forms of transplants showed that total cost is still over AUD 71 000 000, with other forms of transplantation accounting for approximately 25% of total utilisation.

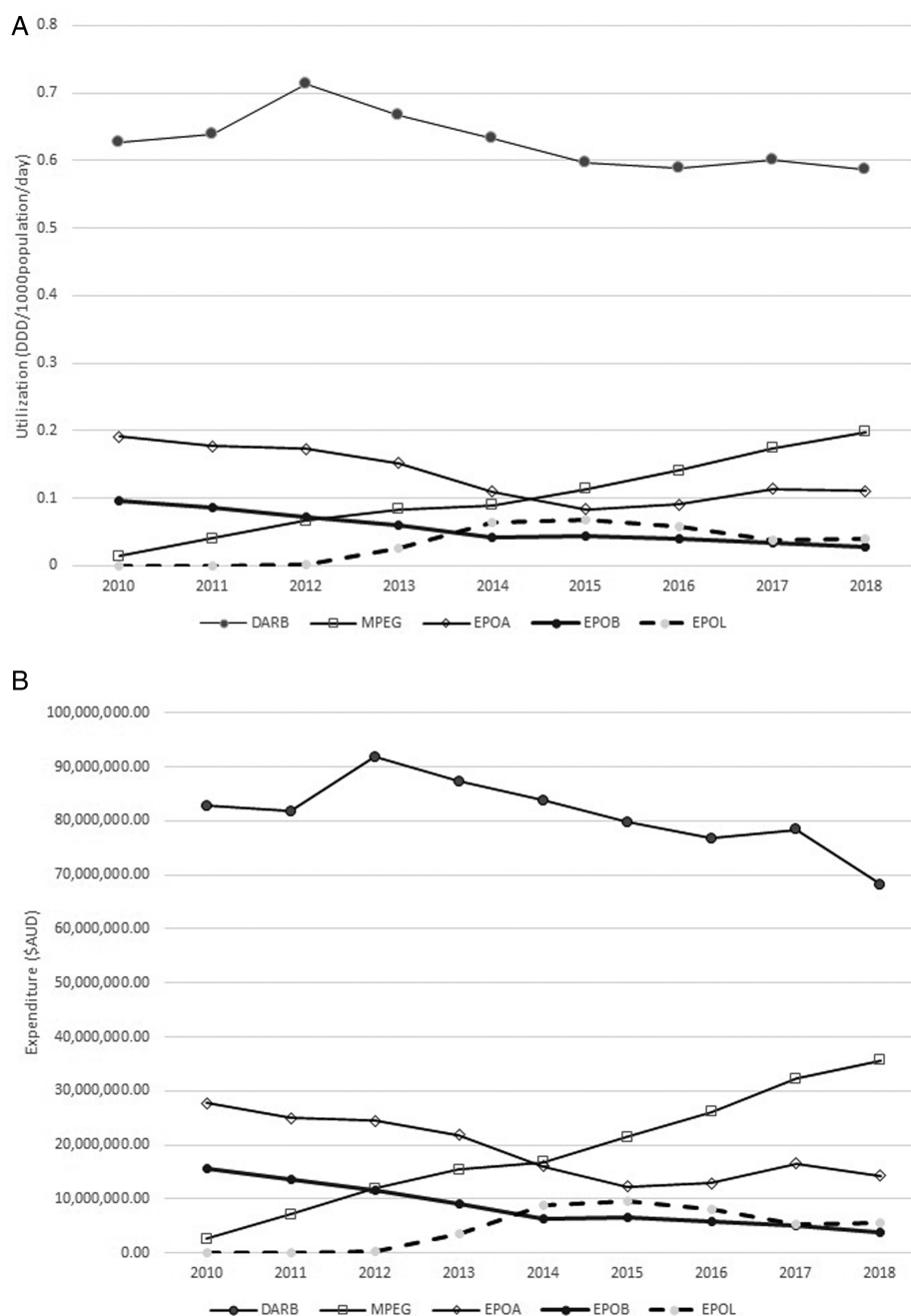
## Discussion

This study is the first to examine the utilisation and expenditure of ESAs while simultaneously offering an update to the understanding of immunosuppressant utilisation and expenditure in Australia. This study captured complete dispensing use and costs for all subsidised ESAs and maintenance immunosuppressant therapies from 2010 to 2018. Utilisation and expenditure on immunosuppressants have continually increased over the study period, whereas the use of ESAs has remained relatively stable.

MPEG was the only ESA to have a consistently increasing utilisation, its DDD/1000 population per day grew an average of 0.022 each year. Its initially low uptake was due to it only being registered by the Therapeutic Goods Association in 2009 and by 2015 it was the second most commonly used agent behind DARB. The concurrent decline in the use of short-acting EPO formulations reflects a tendency towards the prescribing of longer-acting agents. It is still unclear if these long-acting ESAs yield better patient outcomes than short-acting agents and what the overall impact on quality of life is, but patients likely have a preference for less frequent dosing.<sup>[23]</sup>

after the increasing use of MPEG was a large increase in its expenditure. EPO-L's expenditure rose from its release in 2010 through to 2015, before declining. All other ESA had consistent declining expenditure reflecting the general decline in their use. The increasing costs of MPEG have offset the decrease in expenditure across other ESAs, keeping overall expenditure in 2010 and 2018 within 1% of each other, despite the increasing number of people with CKD.

The combined results of all ESA utilisation show that although the use of short-acting ESAs has declined, the increasing uptake of fast-acting agents has offset this, keeping cumulative utilisation across all ESAs relatively constant. That said, this plateau is despite increasing CKD diagnoses<sup>[2]</sup> possibly suggesting a declining trend in the proportion of CKD patients receiving ESA therapies. This may have been contributed to by landmark trials released between 2006 and 2009 which demonstrated that targeting moderate to high haemoglobin levels with ESAs increased the risk of cardiovascular events.<sup>[24-26]</sup>



**Figure 1** Utilisation (DDD/1000 population per day) (a) and expenditure (b) associated with subsidisation of erythropoietin stimulating agents in Australia through the benefits schemes from 2010 to 2018.

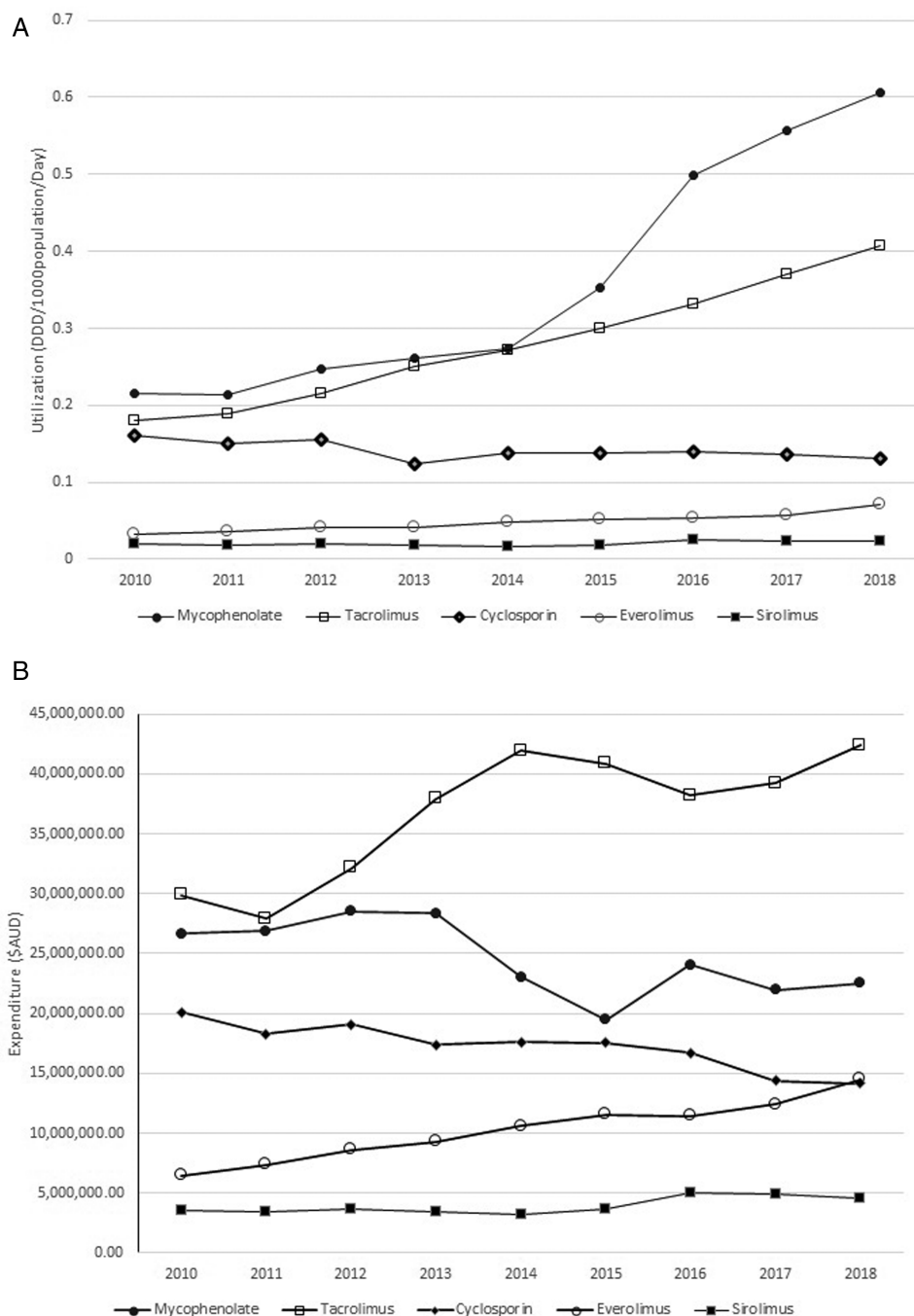
DARB, darbepoetin alfa; MPEG, methoxy polyethylene glycol-epoetin beta; EPOA, epoetin alfa; EPOB, epoetin beta; EPOL, epoetin lambda.

Following these, in 2007 the Food and Drug Administration issued a black box warning on ESAs, for the increased risk of serious adverse events and death associated with targeting high haemoglobin<sup>[27]</sup> and in 2012 the Kidney Disease: Improving Global Outcomes (KDIGO) group updated their guidelines to suggest only starting ESA therapy when haemoglobin levels are between 9.0–10.0 g/dL and to not maintain haemoglobin above 11.5 g/dL<sup>[28]</sup>.

Some international drug utilisation studies regarding ESAs have reported declining use over the last few decades;<sup>[29, 30]</sup> which is often attributed to the publications of trials regarding the safety of ESAs.<sup>[24–26]</sup> Although those looking at ESA use in more recent years have noted that their use has started to level out.<sup>[31]</sup>

Everolimus, sirolimus, tacrolimus and mycophenolate all showed an increase in their utilisation, the greatest of which being for mycophenolate and tacrolimus. This is in line with current KDIGO guidelines which suggest tacrolimus be the first line calcineurin inhibitors and mycophenolate be the first line anti-proliferative agent used.<sup>[11]</sup> This is supported by research highlighting improved graft survival using tacrolimus rather than ciclosporin<sup>[32]</sup> and studies demonstrating the benefit of mycophenolate in combination immunosuppressive therapies.<sup>[33, 34]</sup>

Total expenditure on immunosuppressants consistently increased over the study period and is approaching AUD 100 million per year. The expenditure trends for each agent followed the same pattern as



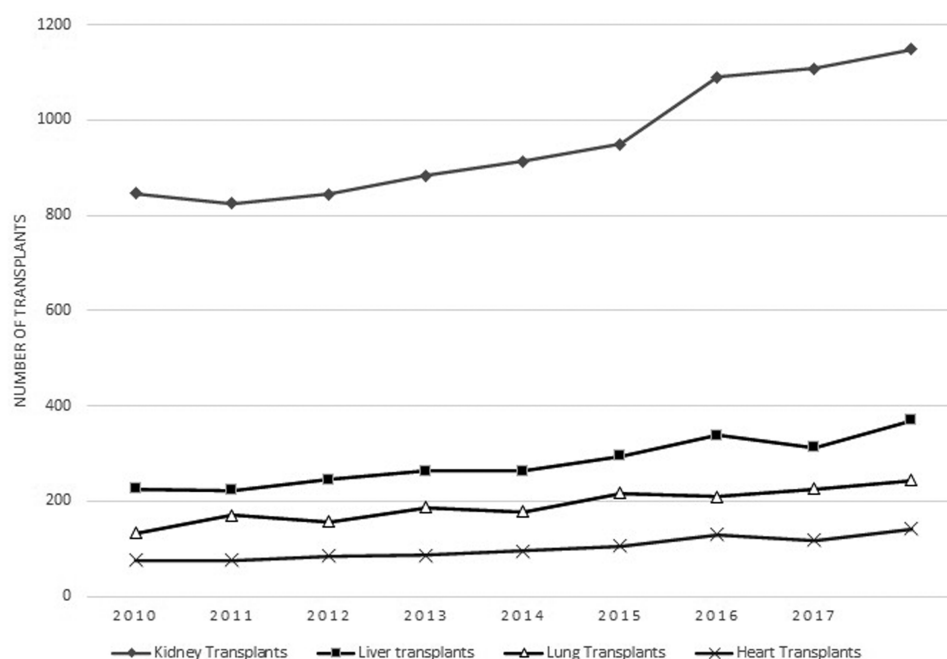
**Figure 2** Utilisation (DDD/1000 population per day) (a) and expenditure (b) associated with subsidisation of immunosuppressive agents in Australia through the benefits schemes from 2010 to 2018.

their utilisation, with the major exception of mycophenolate. Over the study period, there were changes to the PBS's dispensed price for maximum quantity (DPMQ) of mycophenolate. In 2010 the DPMQ for mycophenolate mofetil 250 mg capsules and 500 mg tablets was \$627.81, by 2018 this had dropped to \$153.21. So, although utilisation of these agents increased over the study period, expenditure on them decreased.

In 2015 enteric-coated mycophenolate sodium was changed to an unrestricted benefit meaning it was not possible to distinguish between prescribing for lupus nephritis or post-transplantation immunosuppression. Although, sensitivity analysis showed that the use

of these formulations for lupus nephritis accounted for less than 1% of total mycophenolate use in 2014 and 2013. Therefore, although from 2015 use in lupus nephritis would have been characterised, it was not likely to be of significance.

This study has some limitations. Australian data examined in this study were collected from an administrative database for tracking pharmaceutical dispensing, rather than the actual utilisation of these agents. As such, these data lack information relating to patient characteristics and outcomes. The data indicate dispensed medication and prescriptions filled, but medications not taken by the patient are not accounted for. Furthermore, these data assume that the



**Figure 3** Number of kidney, liver, lung and heart transplants performed per year in Australia.

maximum quantity of medication was dispensed each time, which overlooks situations where smaller quantities may have been dispensed. It also doesn't account for private prescribing and dispensing of these drugs, although given the high cost and ready availability of public subsidised prescriptions, there are likely few private prescriptions. HSD data was also missing for the first half of 2014 and so averages of the end of 2013 and end of 2014 had to be used.

Not all medications used in the management of post-transplantation immunosuppression were characterised in this study. Prednis(ol)one was excluded as it has many indications which cannot be separated using PBS codes. Furthermore, given its low cost, it is primarily patient-funded, rather than government-funded which makes gathering subsidisation data difficult. Similarly, azathioprine is primarily used for indications other than post-transplant immunosuppression and has quite a low cost so therefore was also excluded.

## Conclusion

The number of transplants being performed per year and the number of people living with functional grafts in the community has been increasing in Australia. Because of this the utilisation of immunosuppressant medications is increasing, as is the governments' expenditure on them. Conversely, there was not an observed increase in our expenditure on ESAs, and for most agents, there was a decline in utilisation. Information obtained in this study provides a baseline for rational projection of future use and costs.

## Supplementary Material

Supplementary data are available at *Journal of Pharmaceutical Health Services Research* online.

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## Author Contributions

Study Design and conceptualisation was completed by I.K.S., C.E.S with input and assistance from K.M.G. Data collection and analysis was performed by K.L.S., I.K.S with input from K.M.G. Data interpretation was collaboratively performed by all authors. Manuscript drafted by I.K.S. All authors commented on, reviewed, and edited versions of the manuscripts. All authors read and approved the final manuscript.

## Conflict of Interest

The authors have no conflicts of interest or funding to declare.

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