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Treatment of insomnia, restless legs, cramps, and pain associated with chronic kidney disease: results from a multinational survey of kidney supportive care practice

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Abstract

Background Kidney failure is associated with a high symptom burden, yet few studies describe real-world management approaches.

Methods Kidney care units in Australia, New Zealand (NZ) and the United Kingdom (UK) were surveyed regarding their pharmacological treatment of a range of common symptoms affecting those with kidney failure. The present report describes the results for insomnia, restless legs syndrome (RLS), cramps, and pain. Variation in responses was described using normalised generalised variance (NGV), resulting in a score from 1 (most diverse) to 0 (least diverse).

Results One hundred and twelve (of 171 contacted) kidney units responded, including 56 units in Australia (50%), 7 in NZ (6%), and 49 in the UK (44%). Diversity of practice was highest for insomnia (mean NGV 0.95, range 0.93–0.98), where melatonin was the leading first-line agent (38%), followed by zolpidem and zopiclone (29%). Diversity of practice was lowest for RLS (mean NGV 0.66, range 0.30–0.99), owing to widespread use of iron replacement as first line (69%), gabapentinoids (45%), and dopamine agonists (37%). Diversity of practice was moderate for neuropathic pain (mean NGV 0.71, range 0.44–0.93), cramps (mean NGV 0.72, range 0.48–0.97), and opioids (mean NGV 0.88, range 0.75–0.97). Numerous significant between-country differences in treatment preferences were noted.

Conclusions There is wide variation in treatment approaches to common symptoms affecting people living with advanced CKD or kidney failure, both within and between countries, indicating a need for evidence-based guidelines and further randomised studies to inform practice.

Clinical trial number Not applicable.

Keywords Kidney supportive care, Chronic kidney disease, Insomnia, Restless legs, Pain, Cramps

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Background

Kidney supportive care (KSC) focuses on improving quality of life for people with advanced kidney disease and their families. It is increasingly recognised as an integral part of routine care for people with chronic kidney disease (CKD), and especially those with kidney failure (whether receiving kidney replacement therapy or not) [1]. Patients with kidney failure experience significant symptom burden, particularly the elderly and those with multiple comorbidities. Between 20 and 70% of people with kidney failure report symptoms including restless legs syndrome (RLS), cramps, and insomnia [2, 3]. The prevalence of pain in people with kidney failure has been found to be similar to that amongst those with advanced cancer [4].

Despite how prevalent these symptoms are, their presence and impact on wellbeing is often underestimated and often sub-optimally treated by kidney care providers [3, 5–8]. One important barrier for clinicians in the management of CKD symptoms is the paucity of high-quality evidence to guide treatment [7, 9, 10]. In particular, there are limited studies on safe and efficacious pharmacological treatments to use for symptoms in the context of reduced kidney function and there are no consensus evidence-based guidelines for symptom management [5, 11, 12]. Anecdotally, a wide variety of treatments (typically off-label) are being used, but the range of pharmacotherapies employed to manage common symptoms in people with kidney failure has never been systematically described. We report a survey of kidney units seeking to determine the usual pharmacological management of insomnia, RLS, cramps, and pain for people living with kidney failure across three countries – Australia, New Zealand (NZ), and the United Kingdom (UK).

Methods

Study design

An observational cross-sectional online survey was used to describe the pharmacological management of symptoms in CKD. This was part of a larger project that also explored models of KSC for adult patients, which has previously been reported [13]. The study had institutional ethics approval from the University of Sydney (HREC 2021/851) prior to commencement. Using the Research Electronic Data Capture (REDCap) application [14, 15] hosted by the University of Sydney, the survey was designed by kidney care clinicians in Australia, NZ, and the UK to obtain relevant clinical practice data. In March 2022, a pilot survey was launched across four KSC services. We sought written feedback to ensure readability, feasibility, and face-validity prior to final survey dissemination.

Participants were asked to answer about pharmacological treatments used at their unit to manage various symptoms in people with advanced CKD or kidney failure, including people receiving kidney replacement therapy (KRT), people not yet receiving KRT but planning for it, and those receiving conservative kidney management. The symptoms presented in this study are insomnia, RLS, cramps, neuropathic pain and non-neuropathic pain (use of opioids). Data on treatment of pruritus is described elsewhere [16] and data on altered taste, fatigue, and nausea will be presented separately. Respondents were asked to define typical usage for each pharmacotherapy at their unit into one of five categories: first line, second line, for refractory symptoms only, rarely used or never used. The three initial categories were intended to capture treatments on an implied treatment ladder with rarely used capturing treatments outside of a unit's accepted therapeutic repertoire, but which might be used in exceptional circumstances. Respondents had the option of adding general comments relating to each symptom and to add up to two other therapies using free text and defining their usage. Respondents were directed (where relevant) to assume that non-pharmacological measures had been trialled. Participants were also asked whether their unit had a KSC service. A KSC service was defined as, "an individual or team [working within the larger nephrology unit] dedicated to the management of symptoms and quality of life issues among those with advanced kidney disease". In a separate section following the symptom questions, participants were asked if medicinal cannabis / cannabinoid products were prescribed at their unit (and, if so, for what symptom/s).

Study population

Recruitment and survey responses took place between April to December 2022. Using information available from the Australia and New Zealand Dialysis and Transplant (ANZDATA) registry [17] and the UK Kidney Association (UKKA) registry [18], all kidney care units were systematically identified. In all three countries, kidney care units comprise a nephrologist-led clinical team, typically hospital co-located, delivering dialysis services along with outpatient care of people with CKD and kidney failure. Units are exclusively government-funded in UK and NZ. Most Australian units are similarly funded, although a minority of units are owned and managed privately. Heads of units or heads of KSC units were contacted directly via email with an invitation to complete the survey, with a centre-specific survey link. Participation in the survey implied consent and data were de-identified and stored confidentially. One response was accepted per unit; and the survey link could be shared between staff to promote contributions from multiple clinicians working in each unit.

Statistical analysis

Data were included in the present analysis from all units that contained at least one response within at least one of the included symptom categories. Similarly, denominators within each symptom category refer to the number of units providing at least one response relevant to that symptom. 'Never used' was imputed where no response was made for a particular treatment when participants had otherwise provided at least one response for other treatments in that symptom category. The following treatments were surveyed as individual treatments but combined for analysis: gabapentin and pregabalin as 'gabapentinoids'; zolipidem and zopiclone; amitriptyline and nortriptyline; and levodopa, pergolide, pramipexole, ropinirole, and rotigotine as 'dopamine agonists'. Data were analysed descriptively, with Fisher's exact test used to identify significant differences between countries, and between units that reported having a KSC service and those that did not. A threshold for statistical significance was defined as a p-value of 0.05. No adjustment was made for multiplicity of testing.

The degree of practice variation observed for each treatment was quantified using 'generalised variance'. Generalised variance is a measure of diversity of responses to a categorical variable which reflects the probability that two randomly selected responses would report *different* categories. In the present study, where medication use is described by five categories, generalised variance ranges from 0 (least diverse, all responses are in the same category) to 0.8 (most diverse, each category has an equal share of responses) [19]. For ease of interpretation, this range was normalised (by dividing by the maximum value) to produce normalised generalised variance (NGV) ranging from zero (minimum diversity) to 1 (maximum diversity). The NGV was calculated for each therapy (or therapeutic category) and the mean and range of NGV is presented for each of the four classes of symptoms. For the present study low variation was defined as NGV < 0.7, moderate as 0.7 to 0.89, and high as ≥ 0.9. A more detailed discussion of generalised variance is found in the Supplementary Material. Analysis was performed in Stata 17.0 (StataCorp. College Station, TX).

Results

The survey was emailed to 171 units and 112 responses were received giving a response rate of 66%, comprising 56 (50%) units from Australia, 7 (6%) units from NZ, and 49 (44%) units from the UK. Sixty-three (67% of 96 respondents) units had a KSC service. Median unit size (in terms of number of hemodialysis recipients) was 190 (interquartile range 76–369). Responders were primarily nephrologists (55 [72%] of 76 who indicated their professional category) and nurses (37 [49%]). Additional information on units and their delivery of KSC has been published previously [13]. Fig. 1 describes usage patterns for all symptoms.

Diversity of practice was highest in the treatment of insomnia (mean NGV 0.95, range 0.93 to 0.98) where melatonin was the most commonly used first line agent (40 [38%] of 105 respondents) followed by zolpidem and zopiclone (30 [29%]). Conversely, 42 (40%) and 55 (52%) units (respectively) rarely, or never, used these therapies. Mirtazapine, antihistamines, and benzodiazepines were all commonly used as second line therapies (27 [26%], 27 [26%], and 26 [25%], respectively).

Diversity of practice was lowest for RLS (mean NGV 0.66, range 0.30 to 0.99). This was driven largely by widespread use of iron replacement as the first line therapy (71 [69%] of 103 respondents) and very low use of vitamins C or E (each first or second line at 3 [3%] units). Gabapentinoids and dopamine agonists were both widely used, although with greater diversity of practice seen in the relatively even split between first and second line use (46 [45%] and 36 [35%] for gabapentinoids, and 38 [37%] and 37 [36%] for dopamine agonists) and the minority of units where these agents were rarely or never used (9 [9%] and 16 [16%], respectively). Dopamine agonists and clonazepam were more commonly used in Australia and New Zealand ($P = 0.001$ and 0.009, respectively).

Diversity of practice was moderate on average for neuropathic pain (mean NGV 0.71, range 0.44 to 0.93). There was relative uniformity of practice with first line use of gabapentin predominating (84 [79%] of 106 respondents) and first line use of amitriptyline or nortriptyline also common (50 [47%]). Doxepin was little used (90 [85%] rarely or never used). Diversity of practice was, however, high for duloxetine (36 [34%] first or second line compared to 57 [54%] rarely or never used).

There was also moderate diversity in use of opioids for non-neuropathic pain (mean NGV 0.88, range 0.75 to 0.97). Oxycodone was the most common opioid for non-neuropathic pain (45 [42%] first line and 39 [37%] second line of 106 respondents). Transdermal opioids, buprenorphine or fentanyl, were commonly used, predominantly as second line treatments (41 [39%] and 42 [40%], respectively). Substantial diversity of practice was seen with hydromorphone and tramadol (NGV 0.91 and 0.97, respectively), both being relatively common first or second line treatments, but rarely or never used by a similar proportion of units. Codeine, fentanyl lozenges, and tapentadol were less often used. Methadone and morphine use was uncommon.

Moderate overall diversity in treatment was also evident in the management of cramps (mean NGV 0.72, range 0.48 to 0.97). Magnesium was the most common first line therapy (54 [49%] of 110 respondents). There was a high degree of diversity in the use of quinine (NGV 0.94) and gabapentin (NGV 0.97), with both being

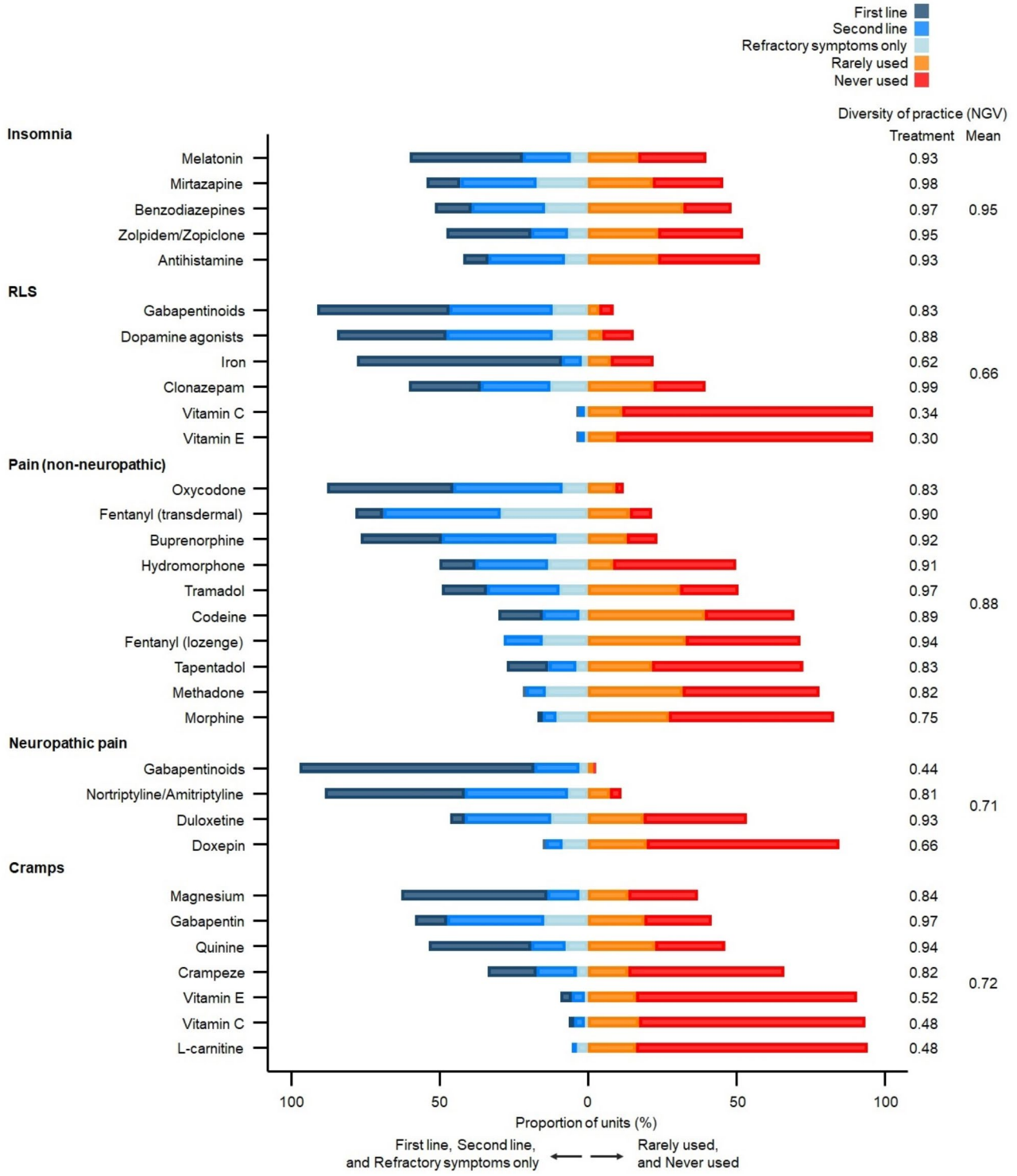

Fig. 1 Use of therapies for insomnia, RLS, neuropathic and non-neuropathic pain, and cramps. Additional pharmacotherapies were indicated by free text, with number of respondents in parentheses. Insomnia: quetiapine (1). RLS: magnesium (2), methadone (1), quinine (1). Non-neuropathic pain: non-steroidal anti-inflammatories (if anuric) (2), alfentanil (1), cannabinoids (1), dihydrocodeine (1), intranasal fentanyl (1), ketamine (1). Neuropathic pain: Topical lignocaine (3), carbamazepine (2), buprenorphine (1), cannabinoids (1), ketamine (1), methadone (1), mexilitine (1), tapentadol (1), topical capsaicin (1), topical menthol (1). Cramps: clonazepam (5), intravenous dextrose (during hemodialysis) (4), pregabalin (3), magnesium (Epsom salts) (1), quinine (tonic water) (2), vitamin B complex (1). NGV, normalised generalised variance; RLS, restless leg syndrome

common first or second line therapies (51 [46%] and 48 [44%], respectively) but also rarely or never used at many units (51 [46%] and 46 [42%], respectively). After magnesium and quinine, Crampeze (LaCorium Health), a formulation of *Viburnum opulus*, magnesium, and *Ginkgo biloba*, was the third most common first line therapy (18 [16%]). Few units reported use of vitamin C, vitamin E, or carnitine for cramps.

There were numerous significant between-country differences in symptom management (Fig. 2). Treatment of insomnia with melatonin, benzodiazepines, and mirtazapine was more common in Australia as compared to the UK, while zolpidem or zopiclone were relatively preferred in the UK. Clonazepam was more often a first line treatment for RLS in the UK than in Australia and NZ, where it was more often second line or for refractory cases only. Dopamine agonists were commonly used in all countries, however a substantial minority of UK units (9 [19%] of 47 respondents) reported they were never used. There were large differences in use of some opioids, particularly hydromorphone and buprenorphine, never used in NZ and less often used in the UK than in Australia. Similarly, duloxetine was reasonably common as a second line agent for neuropathic pain in Australia but much less often used in NZ or the UK. Finally, large differences were observed in the treatment of cramps, with magnesium and Crampeze being common in Australia and NZ but rarely used in the UK, where quinine was the most common first line treatment.

There were no significant differences in treatment preferences between units with and without a KSC service, except relating to use of benzodiazepines for insomnia, where units with a KSC service were less likely to use these as first or second line agents (17 [27%] of 62 respondents) as compared to units without a KSC service (18 [55%] of 33 respondents, $P = 0.03$).

Ten (9%) units (Australia 6, NZ 2, UK 2) reported that medicinal cannabis products were prescribed 'rarely' for people with CKD (no units reported use of such products 'often'). The indications for use of medicinal cannabis products (and number of units reporting use for this indication) were neuropathic pain (7), non-neuropathic pain (5), insomnia (2), RLS (1), as well as for nausea and vomiting (5), anorexia (2), anxiety (2), fatigue (1), and pruritus (1). In all instances, units reported using these products for refractory symptoms only or rarely.

Discussion

This study reported wide variation in treatment of insomnia, pain, cramps, and RLS associated with kidney failure. Variation was seen both between individual units and between countries, with clinically relevant variation in practice evident for all symptoms. Variation in treatment was most pronounced with insomnia pharmacotherapy. Melatonin was most widely used and has been shown to effectively improve sleep in hemodialysis recipients in the short term [20], though this effect may not persist at 6–12 months [21]. Some differences, particularly between-country practice variation, may be due to differences in access to particular therapies, yet much remains unexplained. Melatonin remains prescription-only in the UK, and in New Zealand, but regulatory factors cannot explain between-country differences in use of benzodiazepines and non-benzodiazepine hypnotics (zolpidem and zopiclone), which are prescription-only in all three jurisdictions. Benzodiazepines were more often used in the UK than in Australia, where non-benzodiazepine hypnotics appear preferred (both classes were similarly used in New Zealand). Evidence for use of these drugs to treat insomnia in kidney failure is limited to two small randomised studies (totalling 33 participants) providing weak evidence that zaleplon may be superior to placebo [22] and that zolpidem may be inferior to clonazepam [23]. Moreover, zolpidem initiation has been associated with a 70% increase in risk of fall-related fracture (compared with initiation of trazodone) in hemodialysis recipients [24]. Both zolpidem and benzodiazepines have been associated with a 15% greater risk of mortality in this population, although there was evidence that much of this excess mortality was linked to use in a subpopulation with comorbid chronic obstructive pulmonary disease [25]. Direct evidence to evaluate the efficacy of mirtazapine or antihistamines in people with kidney failure is lacking. This situation contrasts with RLS, where four therapies (gabapentinoids, dopamine agonists, iron replacement, and clonazepam) were all widely used (albeit with variation in their priority in the treatment pathway) resulting in a comparatively low generalised variance. The evidence base supporting these practice patterns is more robust than that informing treatment of insomnia, although the near universal absence of use of vitamin C or E for RLS was notable given these therapies are likely to be safe and are supported by two small randomised controlled trials (RCTs) [26].

The moderate overall diversity in management of cramps may be largely explained by striking between-country differences in practice. Use of magnesium and Crampeze is largely confined to Australia and New Zealand, whereas quinine is still commonly first or second line in the UK. Few randomised studies have assessed treatments for cramping in kidney failure patients outside of the context of intradialytic cramps. Small RCTs suggest quinine may be similarly effective as vitamin E [27], however, at the time that this survey commenced the only therapies tested in a placebo-controlled study are vitamin C, E, and their combination (all of which were efficacious) [28]. Meta-analysis of 5 studies of L-carnitine found evidence that it reduces intradialytic cramping

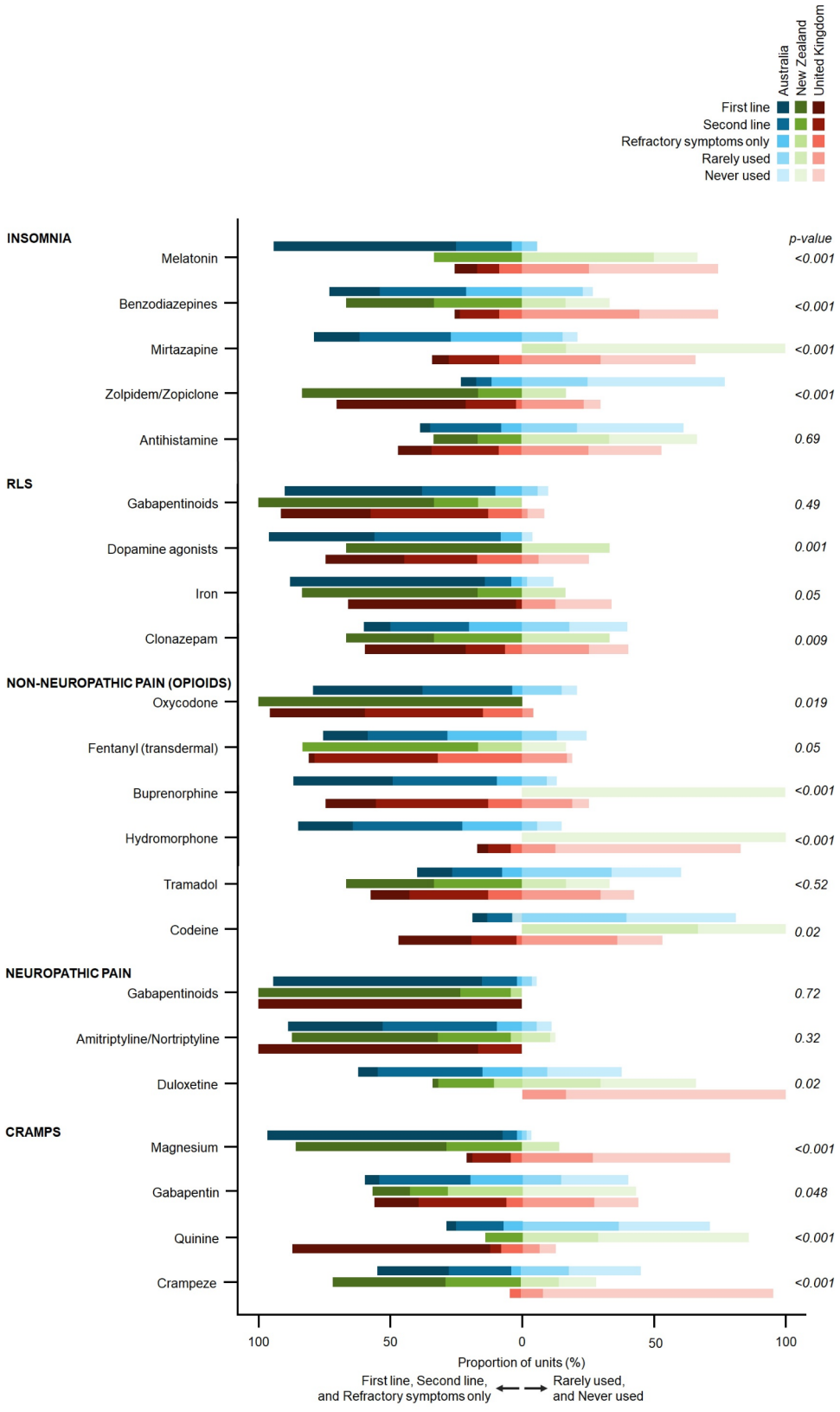

Fig. 2 Variation in symptom management strategies between Australia, New Zealand and the United Kingdom for insomnia, restless legs syndrome (RLS), neuropathic and non-neuropathic pain (opioids), and cramps

[29]. RCTs in the general population have found low to moderate quality evidence that quinine is effective [30] and the evidence for magnesium is mixed [31, 32]. There is no evidence to support the use of Crampeze. The reason for the stark divergence in practice is not clear. Quinine is readily accessible in both Australia and the UK (not in New Zealand), although regulatory agencies in all three countries caution against the use of quinine for muscle cramps owing to the small risk of severe thrombocytopenia [33].

Pain management appeared more consistent across units and between countries, with broad agreement that gabapentinoids, followed by tricyclic antidepressants, were preferred for neuropathic pain - with no evidence of different approaches between countries. There was divergence in opioid use. Oxycodone was the most commonly used analgesic for pain unresponsive to simpler measures, followed by transdermal opioids (fentanyl and buprenorphine). The statistically significant between-country differences in use of these drugs may be explained by differences in accessibility (for example, transdermal fentanyl, but not buprenorphine, is subsidised in New Zealand). However, there were marked differences in use of hydromorphone, which is available in both Australia and the UK (though not New Zealand), yet was little used in the UK. Conversely, codeine is available in all three countries but was significantly more likely to be first or second line in the UK (although, even here there was substantial diversity in use). While no evidence-based consensus guidelines are available, multiple authors recommend against use of codeine in kidney failure and consistently include hydromorphone among lists of preferred opioids for this population [34–36].

Overall, this study found wider than expected variation in the treatment of common symptoms affecting people with kidney failure. While we were unable to ask respondents to explain the reasons behind their treatment preferences, the concordance between the degree of variation within a symptom (as measured by average NGV) and the quantity and quality of available clinical evidence suggests this as an important factor in practice variation. This is clearly demonstrated by contrasting the high variation in management of insomnia, where the evidence base is particularly sparse [37], with the more uniform management of RLS, where iron, gabapentinoids, and dopamine agonists are relatively well supported by evidence in the dialysis population [26] and informed by clear guidelines in the general population [38]. Where evidence is sparse, it appears that prescribing cultures can develop, likely reflecting local opinion leaders and shared training networks, which may explain otherwise unjustified practice variation (examples including the Australian preference for hydromorphone and the shared antipodean favour towards magnesium and Crampeze over quinine). We also identified limited prescription of medicinal cannabis products for this population, primarily for pain. This is consistent with the regulatory restrictions on prescribing and the lack of evidence for efficacy and limited evidence for safety in people with advanced chronic kidney disease [39].

This study has several limitations. Results are based on clinicians' description of their unit's usual management approach, not actual prescribing practices risking self-reporting bias. In addition, respondents may have varied in their interpretation of the response options meaning distinctions between first- and second-line, or refractory use only and rarely used, should not be over-emphasised. Further, clinicians with an interest in symptom management or KSC may have been more likely to complete the survey causing a response bias in the results. Information on reasons behind treatment preferences were not collected and would form a suitable subject for further study. This study was limited to pharmaceutical management and it should be recognised that evidence-based non-pharmacological therapies exist for many common symptoms associated with kidney failure and are typically recommended ahead of pharmacotherapies [40]. Finally, in view of the small numbers of respondents from New Zealand, the inter-country comparisons lack statistical power and should be considered hypothesis-generating only.

Conclusions

This survey revealed substantial variation in management approaches to specific symptoms that significantly impact quality of life in people with CKD; insomnia, RLS, cramps, and pain. While some of this variation is explained by differing treatment availability, much of the variation is unjustified by available evidence. Systematic review and summary of the evidence for symptom management, such as that conducted by the recently released International Society of Nephrology Kidney Supportive Care and Conservative Kidney Management Curriculum [1] may help to inform clinicians but ultimately further randomised studies are required to guide treatment.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12882-025-04107-1.

Supplementary Material 1

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Author contributions
This work was conceived by B.S. and K.D. The survey was designed by E.S., B.S., K.D., B.D.H., D.V.O., N.A., C.M.S., and F.J.C., and conducted by B.S., K.D., B.D.H., C.M.S., and E.S. Analysis was performed by B.S. The manuscript was drafted by K.N. and E.S. All authors contributed to critical review of the manuscript prior to publication.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study had institutional ethics approval from the University of Sydney (HREC 2021/851) prior to commencement. Participation in the survey implied consent and data were de-identified and stored confidentially. The study was performed in accordance with relevant guidelines and regulations.

Consent for publication
Not applicable.

Competing interests
BS has received speakers' honoraria and consulted for CSL Seqirus, and received in-kind research support from IxBiopharmaceuticals.

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