Opioid and Benzodiazepine Use in End-Stage Renal Disease: A Systematic Review

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Summary

Background and objectives Chronic pain and psychiatric disorders are common in dialysis patients, but the extent to which opioids and benzodiazepines are used is unclear. We conducted a systematic review to determine the: (*1*) prevalence of opioid and benzodiazepine use among dialysis patients; (2) reasons for use; (*3*) effectiveness of symptom control; and (*4*) incidence of adverse events.

Design, setting, participants, & measurements Two authors reviewed all relevant citations in MEDLINE/EMBASE/CINAHL/BIOSIS Previews/Cochrane and hand-searched bibliographies. Studies after 1990 reporting prevalence estimates for opioid and/or benzodiazepine use in ≥50 dialysis patients were included.

Results We identified 15 studies from 12 countries over 1995 to 2006. Sample size ranged from 75 to 12,782. Prevalence of opioid and benzodiazepine use was variable, ranging from 5 to 36% (95% CI, 4.1 to 45.5%; $n = 10$) and 8 to 26% (95% CI, 7.1 to 27.3%; $n = 9$), respectively. Prevalence was positively correlated with years on dialysis. Five studies reported on the same cohorts but gave different prevalence estimates. One study verified medication use through patient interviews. Reasons for use were reported in one study. Effectiveness of pain control varied from 17 to 38%, and 72 to 84% of patients with significant pain had no analgesia ($n = 2$). No study rigorously examined for adverse events.

Conclusions The prevalence of opioid and benzodiazepine use in dialysis patients is highly variable between centers. Further information is needed regarding the appropriateness of these prescriptions, adequacy of symptom control, and incidence of adverse effects in this population.

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Introduction

Patients with ESRD on dialysis have a high burden of comorbid disease and markedly reduced quality of life compared with both the general population (1–4) and with patients with other chronic disease states (5). Of all symptoms reported by patients with ESRD, pain is the most common (6). Recent reviews show that 47% of patients with ESRD experience pain (6), and this can be moderate to severe in 82% (7). The etiology of the pain is multifactorial, related to comorbidities (peripheral vascular disease, osteoarthritis, *etc.*), complications of renal failure (bone disease, calciphylaxis, peripheral neuropathy, *etc.*), and the dialysis procedure (needle insertion, osmolar shift cramps, dialysate infusion pain, *etc.*).

Despite its high prevalence, there is little information on whether chronic pain in ESRD is adequately treated. Opioids may be underutilized in patients with renal failure because of concerns about reduced clearance and increased adverse effects (8). Conversely, they may be overutilized for nonsomatic pain that may be more appropriately treated with other agents.

In addition, pain often coexists with depression, anxiety, and insomnia. Almost two of every five dialysis patients experience troubled sleep (6), and 38 to 45% suffer anxiety (6). Treatment of these conditions often results in the concomitant use of benzodiazepines with opioids, potentially increasing side effects. Recommendations regarding the appropriate use of benzodiazepines in ESRD are lacking (9).

To assess the current state of knowledge and inform future research, we conducted a systematic review of the literature on the use of opioids and benzodiazepines in patients receiving dialysis. We sought to determine the prevalence of opioid and benzodiazepine use in ESRD, reasons for their prescription, effectiveness of symptom control, and associated adverse events.

Materials and Methods

Finding Relevant Studies

We performed a comprehensive search of MEDLINE, EMBASE, CINAHL, BIOSIS Previews, and Cochrane Library bibliographic databases from their date of inception to August 1, 2010 for relevant citations in any language. Longitudinal and cross-sectional cohort studies reporting the prevalence of benzodiazepine or opioid prescriptions in ≥50 patients receiving hemodialysis or peritoneal dialysis were included. Randomized trials were not eligible because they do not give reliable estimates of prevalence. Two authors

independently evaluated eligibility, and disagreements were resolved by consensus.

An experienced librarian reviewed the search strategy, which included the terms benzodiazepine, opioid, narcotic, end-stage-renal-disease/ESRD, hemodialysis, peritoneal dialysis, and dialysis. We pilot tested and modified the search strategy iteratively until all articles of known relevance were captured. All of the articles citing included articles as per the Institute for Scientific Information Science Citation Index were reviewed, and we hand-searched the reference lists of the included articles.

Data Abstraction

Using standardized forms, two authors (AW and RR) independently abstracted data from eligible articles on study design, location, baseline patient characteristics, prevalence of opioid and benzodiazepine use, reasons for prescription, effectiveness of symptom control, and adverse events. The authors independently reviewed articles for methodological quality using a modified version of the Newcastle-Ottawa-Scale for quality assessment of observational studies (10) (Table 1). All of the data were reviewed by a third author (RS), and any discrepancies were resolved by consensus.

Statistical Analysis

Agreement between authors regarding article inclusion was assessed using kappa. Baseline characteristics, prevalence estimates, and adverse events for each study population were compiled in tabular format. The 95% confidence intervals (CI) for the proportion of dialysis patients using opioids and benzodiazepines in each study were calculated using the Wilson score method (11). Where multiple studies appeared to report on the same cohort of patients, estimates from the study with the most complete data or highest methodological quality were included in the prevalence estimates. χ^2 tests were used to assess between-study heterogeneity, and the I^2 statistic, which describes the percentage of total variation caused by heterogeneity rather than chance, was calculated (12). Given significant clinical and statistical heterogeneity, prevalence estimates were not pooled. All of the computations were performed in R2.0.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study Selection

Our search strategy yielded >1700 citations, of which 72 full-text articles were retrieved for further evaluation on the basis of abstract and title. Fifteen articles met inclusion criteria (1,7,13–25) (Figure 1). Agreement beyond chance between the two authors for article inclusion was good (kappa = 0.79).

Quality of Included Studies

Inter-rater reliability in the assessment of methodological quality criteria was good (Table 1). Only four studies were specifically designed to examine opioid and/or benzodiazepine use (7,13–15). The data were collected prospectively in all studies, and one retrieved data from an administrative database (16). Patient baseline characteristics and eligibility criteria were reported in the majority of studies, but few described the proportions of patients with missing data. Twelve studies reported on prevalent cross-sections of patients receiving hemodialysis (7,13–15,18–25), whereas three restricted inclusion to patients starting hemo- or peritoneal dialysis in the last 3 months (1,16,17). One opioid study restricted prevalence estimates to the 50% of patients reporting ongoing pain (7). One study verified actual medication use

Table 1. Quality of included studies

	Number of Studies (Total = 15)
Representativeness	
study sample represents the community of dialysis patients well	13 (87%)
study collects data prospectively	13 (87%)
comparison cohorts, if present, are drawn from the same source	3 (20%)[a]
study reports clear inclusion and exclusion criteria	14 (93%)
study measures actual use of opioids and benzodiazepines (*versus* prescription)	1 (7%)
study includes prevalent and incident patients	6 (40%)
all patients in the study are accounted for, and attrition was <20%	4 (27%)
Results	
study reports baseline characteristics (*e.g.*, age, gender, comorbidities)	14 (93%)
study reports reasons for prescription of opioids and benzodiazepines	1 (7%)
study reports effectiveness of opioids and benzodiazepines	2 (7%)
adverse events associated with opioid/benzodiazepine use reported	7 (47%)

[a]Comparison cohort not applicable in the other 12 studies.

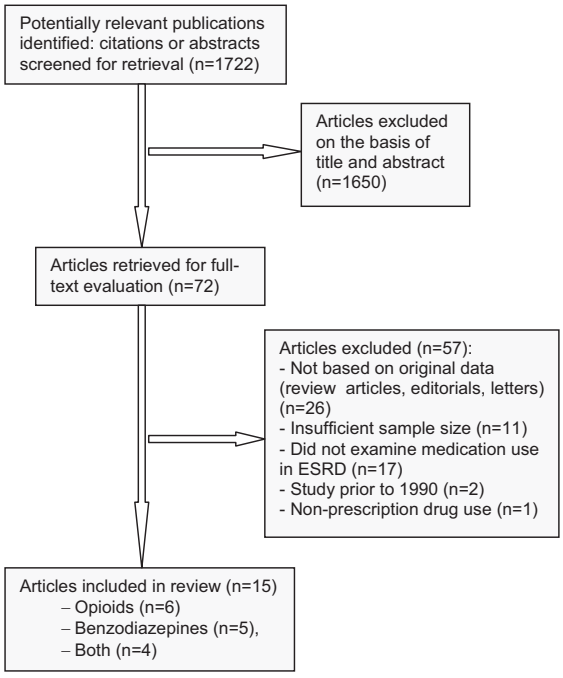

Figure 1. | **Flow diagram of included studies.**

through patient interviews (18), and two reported the effectiveness of symptom control (7,13). Ten studies examined for associations between opioids or benzodiazepines and at least one potential adverse effect (14,16–17,19–20,22,23), but none rigorously examined for these.

Patterns of Opioid Use

Ten studies described opioid use in dialysis patients (1,7,13,17,19–21,23–25). Five were from the United States (1,13,17,24,25), one was from Canada (7), and one was from Belgium (19). The remaining three included cross-sections of patients from between 7 and 12 countries (Dialysis Outcomes and Practice Patterns Study [DOPPS] I and II) (20,21,23). Two of the DOPPS I studies reported on similar cohorts of patients (20,21) (Figure 2). In total, there were >26,000 unique patients from 1995 to 2004, and >90% of these patients were receiving hemodialysis. Patient baseline characteristics from all of the studies are summarized in Table 2.

The prevalences of opioid use in individual studies were variable and ranged from 5% (95% CI, 4.1 to 5.4%) to 36% (95% CI, 27.3 to 45.5) across unique cohorts. The variability among studies was larger than would be expected by chance alone ($P < 0.001$, $I^2 = 98\%$). Eliminating studies that restricted inclusion to those with pain (7) or incident patients (1,16,17) did not narrow the prevalence range substantially (8 to 21%; 95% CI, 7.1 to 23.5%). Interestingly, estimates that appeared to be obtained from the same cohort of patients were not always similar. Bailie *et al.* (21) reported a prevalence of 9% (95% CI, 8.9 to 10.1%) in DOPPS I from 1996 to 2001, whereas Elder *et al.* (20) reported an estimate of 28% (95% CI, 27.1 to 29.3%) from the same database as of 2000. These variable prevalence estimates did not correlate with time period, dialysis vintage, or sample size (data not shown).

The most commonly prescribed narcotic was propoxyphene in combination with acetaminophen in a United States study (13), as compared with codeine and oxycodone in a Canadian study (7). Duration of narcotic use averaged >12 months for 50% of patients and >36 months for another 25% (13).

The reasons for opioid use were examined only in the Canadian study, with musculoskeletal pain found to be most common (65%), followed by dialysis procedure-related pain (14%), peripheral neuropathy (15%), and peripheral vascular disease (10%) (7). Effectiveness of pain control with opioids varied between the two studies examining this outcome. Davison (7) found 38% (95% CI, 29.1 to 47.5%) of patients on weak or strong opioids still reporting pain of moderate to severe intensity within the last 24 hours, whereas Bailie's estimate approached 17% (95% CI, 13.6 to 21.3%) for similar intensity pain experienced over the last 4 weeks (13). Opioid use was positively correlated with time on dialysis (odds ratio [OR] 1.04 per year, $P < 0.0001$) (13). It was also more likely among women (OR 1.11, $P < 0.0001$) and patients with cardiovascular disease (1.21, $P = 0.008$), cancer

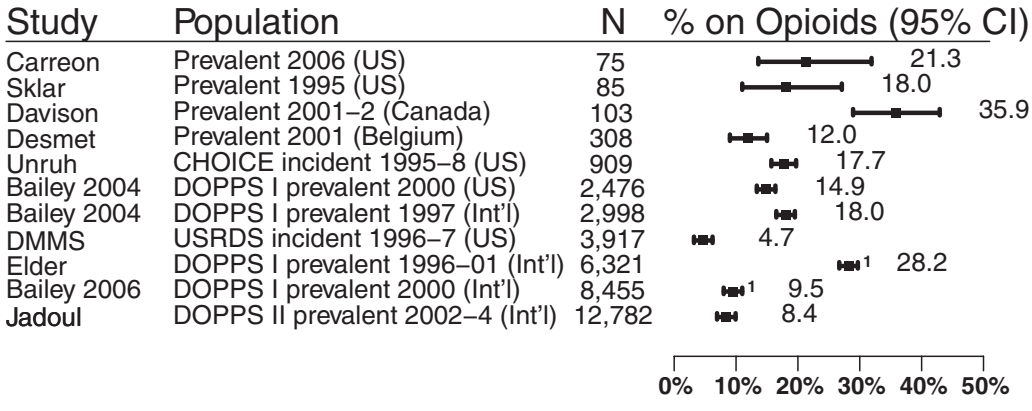

Figure 2. | **Prevalence of opioid use.** 1 indicates studies that overlap in time and population.

Table 2. Baseline characteristics of study populations

	Study	Period	Country	Population	Dialysis Units	*N*	Dialysis Duration (years)	Mean Age (years)	Male (%)	Comorbidities				Benzodiazepine Use				Opioid Use				
										Black (%)	HT	CVD	PVD	DB	*N*	%	Lower 95% CI	Upper 95% CI	*N*	%	Lower 95% CI	Upper 95% CI
Opioids																						
Elder (2008)	1996–2001	Intl.	DOPPS I prev.	308	6321	3.15	59 ± 14.5	58	15	72.5	14.0	19.6	30.0					1782	28.2	27.1	29.3	
Bailey (2006)	2000	Intl.	DOPPS I prev.	308	8455	4.9 ± 5.4	60 ± 14.7	57	38	73.1	15.4	21.3	32.9					803	9.5	8.9	10.1	
Bailey (2004)	1997	US	DOPPS I prev.	142	2998	3.4 ± 3.8	60.6 ± 15.5	53	38	84.1	18.3	26.2	46.2					538	18.0	16.7	19.4	
	2000	US	DOPPS I prev.	142	2476	3.4 ± 3.8	60.6 ± 15.5	53	38	84.1	18.3	26.2	46.2					368	14.9	13.5	16.3	
Desmet (2005)	2001	Belgium	Cross-section	7	308	2.3	67 ± 13.9	56	—	—	12.0	—	27.3					37	12.0	8.8	16.1	
Davison (2003)	2001–2002	Canada		4	103	3.75 ± 3.2	60 ± 15.9	58	1.5	55.6	10.2	10.7	37.1					37	35.9	27.3	45.5	
Carreon (2008)	2006	US	Cross-section	3	75	4.4 ± 5.8	59 ± 14	67	—	—	15.0	15.0	53.0					16	21.3	13.6	31.9	
Both																						
Sklar (1996)	1995	US	Cross-section	1	85	2.38	60.5 ± 16.5	59	6	—	—	—	36.4	22	25.9	17.8	36.1	15	18.0	11.0	27.1	
Unruh (2006)[b]	1995–1998	US	CHOICE incident	81	909	0.25	57.8 ± 14.8	53	27					121	13.3	11.3	15.7	161	17.7	15.4	20.3	
DMMS (1998)[a]	1996–1997	US	USRDS incident	1035	3917	0.16	59 ± 16	53	28	>29	—	—	>43	310	7.9	7.1	8.8	185	4.7	4.1	5.4	
Jadoul (2006)	2002–2004	Intl.	DOPPS II prev.	320	12782	—	—	—	—	—	—	—	—	2171	17.0	16.3	17.6	1078	8.4	8.0	8.9	
Benzodiazepines																						
Winkelmayer (2007)[c]	1996–1997	US	USRDS incident	1035	3630	0.16	58.5 ± 15.6	54	29	71.0	10.0	17.3	48.6	408	11.2	10.3	12.3					
Manley (2004)	2003	US	DCI cross-section	200	10474	3.73 ± 4.0	60.2 ± 15.6	52	45	>26.6	—	—	>40.1	2765	26	25.6	27.3					
Manley (2000)	1999	US	Cross-section	2	238	2.83 ± 2.8	59.5 ± 16	53		21.0	—	—	28.0	32	13.4	9.7	18.4					
Fukuhara (2006)	2002–2004	Intl.	DOPPS II prev.	>300	5122									869	17.0	16.0	18.0					
	2002–2004	Japan	DOPPS II prev.	59	1584	—	—	—	—	—	—	—	—	308	19.4	17.6	21.4					
Bailey (2007)	1999	Intl.	DOPPS I prev.	307	4924	5.27 ± 5.6	58.9 ± 14.5	58	17	72.2	13.8	19.5	31.0	741	15.0	14.1	16.1					
	2002–2004	Intl.	DOPPS II prev.	320	7760	5.19 ± 5.6	61.7 ± 14.4	58	9	77.0	16.3	24.9	32.5	1536	20.2	19.3	21.1					

HT, hypertension; CVD, cerebrovascular disease; PVD, peripheral vascular disease; DB, diabetes; Intl., international; prev., prevalent.
[a]1919 peritoneal dialysis patients.
[b]228 peritoneal dialysis patients.
[c]1558 peritoneal dialysis patients.

(OR 1.27, $P = 0.02$), and psychiatric disease (1.37, $P < 0.0001$) (13).

Patterns of Benzodiazepine Use

Nine studies reported on benzodiazepine use in patients on dialysis (1,14–18,22–24). Six of these were from the United States (1,15–18,24), and three were international cross-sections from DOPPS I and II (14,22,23). Three studies reported on the same cohort of DOPPS I patients (14,22,23), whereas two reported on Dialysis Mortality and Morbidity Study Wave 2 patients (1,16). In total, there were >33,000 unique patients from 1995 to 2004, and approximately 90% of these patients were receiving hemodialysis. Patient baseline characteristics are summarized in Table 2.

There was significant clinical and statistical heterogeneity between studies on the prevalence of benzodiazepine use ($P < 0.001$, $I^2 = 99\%$) (Figure 3). In the three unique studies of incident ESRD populations, benzodiazepine use ranged from 8% (95% CI, 7.1 to 8.8%) to 13% (95% CI, 11.3 to 15.7%) (1,16,17). The prevalence across the remaining studies ranged from 13% (95% CI, 9.7 to 18.4%) to 26% (95% CI, 25.6 to 27.3%) (14–15,18,22–24). We found no correlation between prevalence and time period or sample size.

None of the studies examined the reasons for benzodiazepine use or the effectiveness of symptom control. A Japanese study commented on clinically depressed ESRD patients being twice as likely as those in other countries to be prescribed benzodiazepines (32.3% *versus* 15.7%) (14). The most commonly prescribed benzodiazepines in one study were temazepam, lorazepam, alprazolam, and clonazepam (16). Dialysis patients who used benzodiazepines were more likely to be female (53% *versus* 45%, $P = 0.002$), Caucasian (77% *versus* 60%, $P < 0.001$), and have lung disease (OR = 1.43; 95% CI, 1.03 to 1.98) and less likely to have cerebrovascular disease (OR = 0.68; 95% CI, 0.47 to 0.98) (16).

Adverse Effects of Opioid and Benzodiazepine Use

No study rigorously examined for adverse effects from opioid or benzodiazepine use in dialysis patients. However, both opioids and benzodiazepines were reported to be weakly associated with poor sleep quality (17,20). Benzodiazepines were also associated with reduced sexual pleasure and arousal (22). Two studies reported a significant association between benzodiazepine prescription and death in adjusted analyses (14,16), whereas opioids were associated with an increased risk of falls (19) and fractures (23). These relationships, however, are not necessarily causal (Table 3).

Discussion

In this systematic review with more than 26,000 unique ESRD patients, the prevalence of opioid use was highly variable, ranging from 5 to 36% (95% CI, 4.1 to 45.5%). In comparison, United States pharmacy claims suggest that between 17 and 18% of the general population uses opioids (26), and studies of United States veterans place estimates as high as 33% (27). The reported opioid use in ESRD patients is much lower than we expected, considering that patients on dialysis report significantly higher pain and worse physical functioning than the general population (1–4,28,29). Individual studies in our review confirm that pain is inadequately managed in this population (7,13,25). This issue deserves attention from nephrologists, because inadequate pain control not only results in poor quality of life but may ultimately lead certain patients to withdraw from dialysis.

One reason that opioids are underutilized in patients receiving dialysis may be physician concerns regarding adverse effects. Opioids may exacerbate symptoms of chronic kidney disease (*e.g.* nausea, vomiting, fatigue, and constipation) and those attributed to hemodialysis (*e.g.* orthostatic hypotension and impaired cognition) (8). They may also cause more serious side effects including central nervous system depression, cardiorespiratory depression, and physical and psychologic dependence (8). The potential for adverse effects is compounded in dialysis patients because of reduced renal clearance of active metabolites, the uremic environment, and the presence of multiple comorbidities. Different classes of opioids may have differential effects in this regard (30,31), but

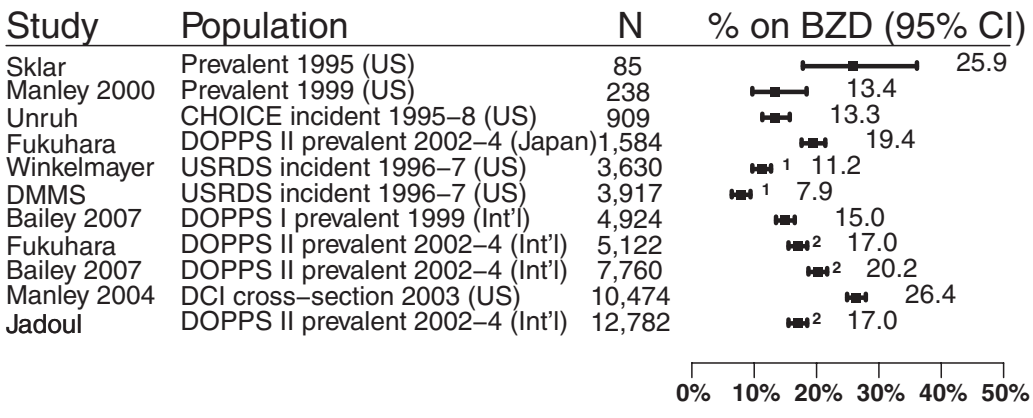

Figure 3. | **Prevalence of benzodiazepine use.** 1 and 2 indicate studies that overlap in time and population.

Table 3. Adverse events associated with opioid and benzodiazepine use

	Risk of Outcome		Study
	With Opioids	With Benzodiazepines	
Poor sleep quality	1.55 ($P < 0.0001$)[a]	1.59 ($P < 0.0001$)[a]	Elder (2008)
	1.22 (95% CI: 0.88 to 1.69)[a]	1.67 (95% CI: 1.15 to 2.44)[a]	Unruh (2006)
Sexual dysfunction (pleasure)	—	1.26 ($P = 0.0078$)[a]	Bailie (2007)
Sexual dysfunction (arousal)	—	1.24 ($P = 0.0134$)[a]	Bailie (2007)
Hip fracture	—	1.0 (0.5 to 2.0)[c]	Winkelmayer (2007)
	1.55 ($P < 0.05$)	1.19 ($P = 0.03$)	Jadoul (2006)
Any fracture	1.67 ($0.01 < P \leq 0.05$)	1.31 ($P = 0.03$)	Jadoul (2006)
Falls	3.7 ($P < 0.001$)[a,b]	—	Desmet (2005)
Hospitalization	—	1.0 (0.9 to 1.1)	Fukuhara (2006)
Mortality	—	1.27 (1.01 to 1.59, $P < 0.04$)	Fukuhara (2006)
		1.15 (1.02 to 1.31)[b]	Winkelmayer (2007)

[a]Odds ratios.
[b]Unadjusted odds ratio.
[c]Hazard ratios (all others are relative risk values).

practitioners may not be aware of these nuances. A fear of potential medico-legal ramifications may reinforce physicians' reluctance to prescribe opioids. A review of the recent April 2009 Canadian Medical Protective Association Risk Identification paper revealed 49 law suits launched in Canada between 2000 and 2007 because of alleged inappropriate opioid prescription and associated adverse events, but only one of these decided against the prescribing physician (32). Fears of litigation may be unfounded in Canada, but the same may not hold true in other jurisdictions.

Although opioids may be underutilized in some patients, they may be prescribed inappropriately in others. The reasons for prescription of opioids in ESRD patients are not always clear, as was suggested by our review. We found only one study that reported reasons for opioid prescription; almost half of the patients had conditions that may not respond to opioids (7). Attempted treatment of perceived pain from conditions such as restless legs and neuropathy with opioids rather than more appropriate agents such as gabapentin could result in continued functional limitation of patients and high levels of undertreated pain.

There are no clear guidelines or randomized trials on the appropriate management of chronic pain in ESRD. This is likely the major factor contributing toward both the under- and overprescription of opioids in this population (7,8,13,33). The World Health Organization recommendations for opioid therapy in acute and chronic malignant pain exist, but it is uncertain whether these can be extrapolated to nonmalignant pain and to patients with ESRD (34,35). The need for specific guidelines to treat pain in ESRD is paramount, given the potential for increased adverse effects discussed above. Non-ESRD-specific conditions such as fatigue, pain, and depression are as prevalent as ESRD-specific conditions (anemia, renal osteodystrophy, access, adequacy, *etc.*) and thus are deserving of equal attention by guideline committees (36). In fact, the former may be more important to patients than the latter. Furthermore, randomized controlled trials (RCT) assessing the efficacy and safety of opioids in ESRD are needed to inform such guideline development. Although our review included only cohort studies, during our search we were struck by the paucity of RCTs in this field. In fact, we could find no RCTs studying the most commonly prescribed opioids in ESRD. Currently, one group is attempting to address this deficiency (37), but more trials are needed.

The consequences of undermanaged pain have the potential to exacerbate other conditions highly prevalent in ESRD, including insomnia, restlessness, depression, and anxiety. This may result in the use of benzodiazepines for symptom control with further risks of adverse events. Although the use of benzodiazepines in the general population is between 2 and 9% (38–40), the use of these agents appears to be much higher in ESRD. In our review, we found the prevalence of benzodiazepine use to be from 8 to 26% (95% CI, 7.1 to 27.3%). This review also suggests that the use of benzodiazepines increases with time on dialysis, because we found that the prevalence in incident patients was only 8 to 13% (95% CI, 7.1 to 15.7%) (1,16,17). Prescription of benzodiazepines has also become more common in recent years. United States Medicare data show that although there were no significant changes in benzodiazepine prescription frequency among ESRD patients between 1993 and 1997 (1), there was a more than three-fold increase between 1998 and 2003 (8% in 1998 *versus* 26% in

2003) (18,41). The high prevalence of chronic benzodiazepine use may be appropriate to control anxiety and restlessness or less appropriate to treat insomnia. Surprisingly, no studies systematically examined the reasons for use of benzodiazepines in ESRD. One study in our review suggested that benzodiazepines were being inappropriately used to control depressive symptoms in ESRD patients, a practice associated with increased mortality (14). Guidelines on the appropriate use of benzodiazepines in ESRD are thus also needed.

This review highlights a shortage of quality studies examining opioid and benzodiazepine use in ESRD. Only four studies (7,13–15) were specifically designed to examine drug use in dialysis patients. The remainders were large trials of patients from registries that incidentally collected limited data on medication use. Only one study confirmed patient consumption of medications (18), whereas others relied solely on prescription as a surrogate for actual drug use. Less than half reported adverse effects. Included studies were also subject to high attrition rates and showed discrepancies in reported prevalences between studies using the same cohorts of patients, not accounted for by time period, dialysis vintage, or sample size (Figures 2 and 3).

There are limitations to this review. We created a modified version of an existing scale for establishing the methodological quality of included observational studies, because no widely accepted scale exists. Furthermore, studies from different centers used variable methods of data collection and collected data over multiple time intervals, resulting in large variability in prevalences between studies (opioid and benzodiazepine studies, $I^2 = 98$ and 99%, respectively, $P < 0.001$). There were also no studies representing patients from Africa, India, China, the Middle East, or South America, emphasizing gaps in our understanding of global trends in medication use in ESRD.

Conclusions

Inadequately treated pain in ESRD patients is a prognostically important problem that remains poorly understood. Nephrologists are ultimately responsible for treating symptoms in dialysis patients, whether these symptoms are related to ESRD or comorbid disease. Thus, addressing knowledge gaps in this field lies within the purview of the nephrologist. More information is needed on the true prevalence, etiologies, and factors associated with inadequately treated pain and its related symptoms in ESRD. In addition, our review suggests that detailed examination of physician prescription patterns, reasons for use or nonuse of opioids and benzodiazepines, appropriateness of these prescriptions, adequacy of symptom control, and adverse effects in patients with ESRD is required. Such information can be used to guide the development of programs and practice recommendations to improve the management of chronic pain and associated symptoms in ESRD.

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Disclosures

None.

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