

Efficacy of the World Health Organization Analgesic Ladder to Treat Pain in End-Stage Renal Disease

Ahmad S. Barakzoy and Alvin H. Moss

Section of Nephrology, Department of Medicine, West Virginia University School of Medicine, Morgantown, West Virginia

Pain is the one of the most common symptoms experienced by patients with ESRD; it impairs their quality of life and is undertreated. Most pain clinicians believe that the pain management approach of the World Health Organization (WHO) three-step analgesic ladder is applicable to the treatment of patients with ESRD, but this approach has not been validated for them. A cohort of 45 hemodialysis patients were assessed for type and severity of pain using the Short-Form McGill Pain Questionnaire and then treated during a 4-wk period according to the WHO analgesic ladder. Mean age was 65 ± 12.5 yr, and 22 (49%) patients had diabetic nephropathy as the cause of ESRD. Initial pain was rated severe by 34 (76%) patients. There was no difference in initial pain rating by gender, age, race, or type of pain. Forty percent of patients reported nociceptive pain, 31% neuropathic, and 29% both. Adequate analgesia was achieved in 43 (96%) of 45 patients. The mean pain score decreased from 7.8 ± 1.2 to 1.6 ± 1.3 ($P < 0.001$). Patients who were 65 yr and older had higher posttreatment scores than those who were younger than 65 (2.1 ± 1.4 versus 0.94 ± 0.93 ; $P = 0.002$) and more medication adverse effects. It is concluded that the use of the WHO three-step analgesic ladder leads to effective pain relief in hemodialysis patients. Older patients will need more careful pain management to achieve the same results as younger patients. Further studies are needed to confirm these results in a larger, more diverse dialysis population.

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Pain has become an important concern for those who treat patients with ESRD. There is an increasing recognition that pain is one of the most common symptoms experienced by patients with ESRD, that it impairs their quality of life, and that it is undertreated (1–8). Most pain clinicians believe that the principles of cancer pain management as described in the American Pain Society primer (9) and the World Health Organization (WHO) monograph (10) are applicable to the treatment of patients who have ESRD and are in pain. The approach of using the WHO analgesic ladder to treat patients who have ESRD and are in pain has been recommended in two review articles in the nephrology literature (11,12), but it has not been validated prospectively. For this reason, we conducted this study to evaluate the efficacy of using the WHO three-step analgesic ladder to treat pain in patients with ESRD.

Materials and Methods

Study Population

We conducted a prospective cohort study of hemodialysis patients who were receiving standard care for pain and other symptoms between March and May 2005 in two dialysis units under the medical directorship of the West Virginia University School of Medicine Section of Nephrology. To be eligible to participate in the study, patients had to be older than 18 yr, possess decision-making capacity, have no history

of drug abuse and could not have been receiving continuous treatment for chronic pain so that the effect of the treatment intervention could be assessed. All dialysis patients in the two dialysis units who met these inclusion criteria were approached for participation. From those who agreed to participate, we identified patients who were in pain and were willing to undergo assessment and treatment by the study investigators. Patients who completed the pre- and posttreatment evaluation compose the subjects of this study. This study was approved by the West Virginia University Institutional Review Board for the Protection of Human Subjects, and written informed consent was obtained from all participants.

Baseline Characteristics and Instrument for Pain Assessment

Patients' charts were reviewed for demographic data (age, gender, and race), dialysis adequacy, allergies, current medications, drug history, comorbidity, and liver function. We interviewed those who agreed to participate in the study to identify patients who were in pain and willing to undergo treatment, and one of the investigators (A.S.B.) administered the Short-Form McGill Pain Questionnaire (SF-MPQ) to them. This questionnaire was validated previously in patients with cancer, postsurgical, obstetric, and musculoskeletal pain (13,14). The original and longer version of the SF-MPQ, the McGill Pain Questionnaire, has been used successfully in the assessment of patients with ESRD (1). The SF-MPQ consists of 15 descriptors of pain (11 sensory and four affective) that are rated on an intensity scale as 0 = none, 1 = mild, 2 = moderate, or 3 = severe. Three pain scores are derived from the sum of the intensity values of the words chosen for sensory, affective, and total descriptors. In addition, the SF-MPQ includes a present pain intensity visual analogue scale (VAS; 0 through 10) and an evaluative overall intensity of the total pain experience (0 = no pain, 1 = mild pain, 2 = discomforting pain, 3 = distressing pain, 4 = horrible pain, and 5 = excruciating pain). The three pain descriptors are

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Address correspondence to: Dr. Alvin H. Moss, Center for Health Ethics and Law, West Virginia University School of Medicine, PO Box 2022, Morgantown, WV 26506-9022. Phone: 304-293-7618; Fax: 304-293-7442; E-mail: amoss@hsc.wvu.edu

added to the VAS and the evaluative overall intensity to obtain a total score for the SF-MPQ. Patients who selected the sensory descriptors of “burning” and “stabbing” were classified as having neuropathic pain. Patients who selected the sensory descriptors of “aching,” “cramping,” “gnawing,” “sharp,” “throbbing,” and “tender” were classified as having nociceptive pain (15).

Pain Treatment Approach

Pain medications were prescribed according to the WHO three-step analgesic ladder (Figure 1) (10). In previous studies, the use of the WHO three-step analgesic ladder to treat pain has resulted in adequate analgesia in between 69 and 100% of patients (16) and now is recognized as global health policy and one of the major advances in the treatment of patients with pain (17,18). Using the VAS in the SF-MPQ, patients rated their pain on a scale from 0 = no pain to 10 = the worst pain possible. Patients who described their pain as nociceptive and rated their pain between 1 and 4 were considered to have mild pain and were prescribed medications in step 1 of the ladder. Patients who described their pain as nociceptive and rated their pain 5 or 6 were considered to have moderate pain and were prescribed medications in step 2 of the ladder. Patients who described their pain as nociceptive and rated their pain as 7 to 10 were considered to have severe pain and were prescribed medications in step 3 of the ladder. Patients who described their pain as neuropathic were prescribed gabapentin or, when cost of medication was an issue, nortriptyline. Patients were seen weekly for 4 wk, and on subsequent visits, medication dosages were

increased or medications were changed or added until the patients reported a pain score of <5 and satisfaction with their degree of pain relief. Patients with moderate to severe neuropathic pain despite the prescription and titration of gabapentin or nortriptyline had an opioid added. The approach for pain management in this study was similar to that described in Davison’s review of recommended treatment of chronic pain in patients with ESRD (12). Patients were considered to have achieved adequate analgesia when they rated their posttreatment pain as mild or none. At the completion of the treatment period, patients were readministered the SF-MPQ. In this study, pain medications for treatment of patients who had moderate (step 2) and severe pain (step 3) were chosen on the basis of the pharmacokinetics of opioids and their metabolites to ensure use of opioids with a reasonable safety profile in ESRD (11,19).

Statistical Analyses

Patients’ initial and posttreatment VAS pain scores were compared for the entire population, gender, age (<65 versus \geq 65 yr), and race (white versus black) and for patients who reported their pain as nociceptive or neuropathic. Patients’ initial and posttreatment total SF-MPQ scores were compared for the entire population. A *t* test was used for paired and independent samples for continuous variables. Data are presented as means \pm SD. *P* < 0.05 is considered significant.

Results

A total of 143 patients met inclusion criteria; of these, 78 (54%) reported pain. Of the 78 patients, 17 refused to participate in the study because of concerns about medication costs or adverse effects; of these 17, eight reported moderate pain and nine reported mild pain. Sixteen patients who were in pain and already regularly taking pain medicines were excluded because it would not be possible to assess the impact of the WHO analgesic ladder approach in them. Forty-five agreed to participate in the study (Figure 2). Mean age for these patients was 65 ± 12.5 yr. Fifty-three percent were men; 83% were white, and 17% were black. Twenty-two (49%) patients had diabetic nephropathy as the cause of their ESRD. The mean dialysis Kt/V for the 45 patients was 1.56 ± 0.28 .

Of the 62 patients who were in pain and not already regularly taking pain medicine, 53 (86%) reported pain that was moderate or severe. Of the 45 patients in the study, initial pain was rated severe by 34 (76%) patients. There was no difference in initial pain rating by gender, age, race, or type of pain (nociceptive or neuropathic; Figures 3 and 4). Forty percent of patients reported nociceptive pain, 31% neuropathic, and 29% both. Burning was the most frequent descriptor used by patients to report their pain; 25 patients selected it. Twelve patients reported aching pain; 10 sharp pain; five stabbing; four throbbing; and two each cramping, gnawing, and tender. The following descriptors in the SF-MPQ were not selected by any patients: Shooting, heavy, splitting, tiring, sickening, fearful, and punishing.

Adequate analgesia was achieved in 43 (96%) of 45 patients. The mean pain score decreased from 7.8 ± 1.2 to 1.6 ± 1.3 (*P* < 0.001). The two patients in whom adequate analgesia was not obtained were 68 and 74 yr of age. On the overall intensity of the pain experience rating completed at the end of the study, 11 (24%) patients indicated no pain, 32 (71%) patients indicated

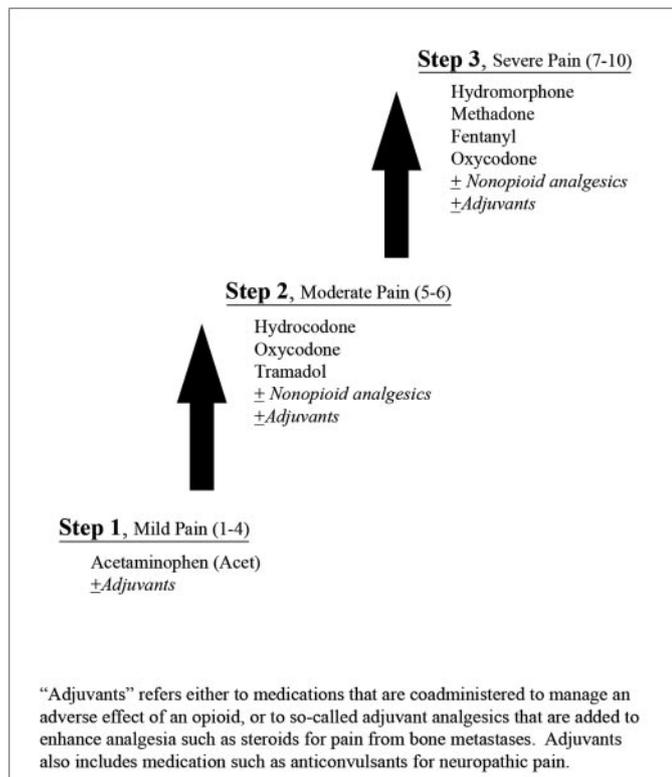


Figure 1. The World Health Organization three-step analgesic ladder modified to exclude drugs unsafe in renal failure. Patients were treated with medications in step 1 when they rated their pain as a 1 to 4 on a 10-point scale. Patients were treated with medications in step 2 when they rated their pain as a 5 or 6 on a 10-point scale. Patients were treated with medications in step 3 when they rated their pain as a 7 to 10 on a 10-point scale.

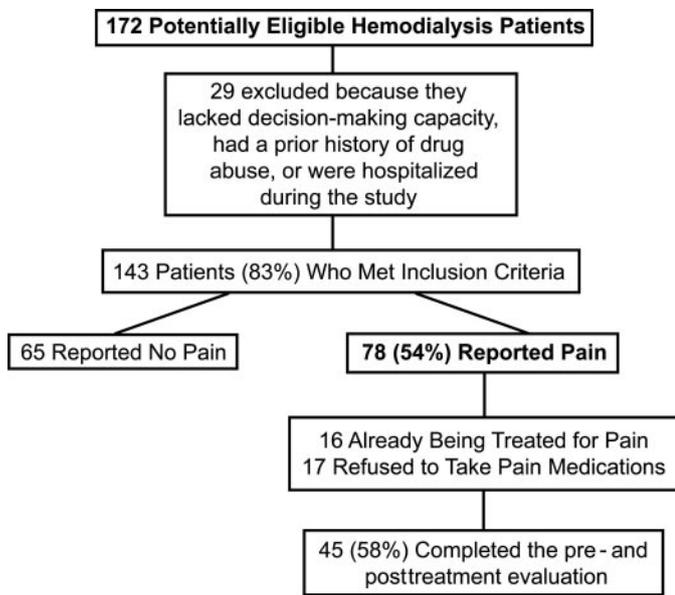


Figure 2. Study participants. A total of 143 of 172 potentially eligible hemodialysis patients met inclusion criteria: 78 (54%) patients reported pain; 45 (58% of the patients in pain) agreed to participate in the study.

mild pain, and two (4%) patients indicated discomforting pain (moderate level). No patients reported pain that was distressing, horrible, or excruciating. Comparable pain relief was achieved for patients with nociceptive and neuropathic pain (Figure 4). Patients who were 65 yr and older had higher posttreatment pain scores than those who were younger than 65 yr (Figure 5). The total SF-MPQ score was reduced from 17.3 ± 3.8 to 4.3 ± 3.0 ($P < 0.001$). The percentages of patients who were treated with particular pain medications were as follows (the numbers do not add up to 100% because 24% of patients were prescribed more than one pain medication): Gabapentin, 38%; hydrocodone, 27%; tramadol, 24%; oxycodone, 20%; nortriptyline, 16%, and propoxyphene, 2%. The use of propoxyphene in kidney disease is not recommended (11); this patient had previously used propoxyphene safely and requested it again. Opioid neurotoxicity was not noted during the study. Adverse effects were observed in three patients, all of whom were older than 65 yr. In two patients, the dosage of gabapentin was reduced from 300 mg at bedtime to 100 mg because of “grogginess” and somnolence. One elderly patient was switched from an oxycodone-acetaminophen combination to tramadol because of dizziness.

A formal assessment of the impact of pain treatment on patients’ quality of life was not conducted, but 22 patients made unsolicited comments. The comments were analyzed and coded into three general domains: More restful sleep, improved function, and better ability to tolerate dialysis. Representative comments were as follows: “I have more energy because I am resting better at night”; “I am able to walk to my mail box, something I could not do before because of hip and leg pain”; and, “I am able to tolerate 4 hr of dialysis without the severe back pain.”

Discussion

This study has four major findings. First, use of the WHO three-step analgesic ladder approach to treating pain led to effective pain treatment in >90% of our hemodialysis patients. Second, we note that treatment of pain is more difficult in elderly dialysis patients. Third, we confirm the high prevalence of pain in the hemodialysis population and undertreatment of pain in the majority of dialysis patients. Fourth, the SF-MPQ was a useful and efficient tool to assess pain in hemodialysis patients.

With the WHO analgesic ladder approach, 96% of our patients were treated adequately on the basis of their posttreatment report of pain. At the conclusion of our study, 43 (96%) of 45 patients reported mild pain at worst, and two reported moderate pain. No patients reported severe pain. These findings indicate that use of the WHO three-step analgesic ladder results in effective pain relief in the vast majority of dialysis patients; these outcomes in dialysis patient pain management are comparable to those for cancer patients and patients with other chronic illnesses (16).

Although elderly patients reported reduction in their pain after treatment to the mild range, their mean pain level at the end of the study was statistically higher than for younger patients; the clinical significance of this finding bears further research. The only two patients who reported more than mild pain at the conclusion of the study both were older than 65 yr. Also, adverse effects from pain medication occurred only in elderly patients. These findings underscore that pain treatment is more difficult in elderly hemodialysis patients as it is in other elderly patient populations (20).

In our study, we identified pain in 54% of dialysis patients. Similarly, in the most comprehensive study of pain in dialysis patients to date, Davison (1) found that 103 (50%) of 205 patients in four Canadian hemodialysis units reported pain. In the Davison study, musculoskeletal pain was the most common type of pain reported (63% of patients), followed by pain related to the dialysis procedure (14%) and peripheral neuropathy (13%). As in our study, in Davison’s study, nociceptive pain was equally severe to neuropathic and responded equally well to treatment.

Our patients were receiving standard care at the time of this study, but only 21% of the patients whom we identified to be in pain were receiving pain medication at the start of our study. Davison’s study found undertreatment of pain in 75% of patients (1). Of the 62 patients who were in pain and not receiving pain medication at the initiation of our study, >80% rated their pain as moderate or severe. Clearly, these patients were being undertreated for pain. How can we account for the widespread prevalence of untreated pain in our population, especially because before our study, the patients were being seen weekly by a nephrologist or a nephrology nurse practitioner? The answer relates to how pain is assessed. Unless our patients were asked explicitly about their pain, they did not report it. This finding is true for other patient populations as well (21,22). The implication of this finding is that for dialysis patients to receive adequate treatment for their pain, an explicit pain assessment must be part of the treatment that they receive.

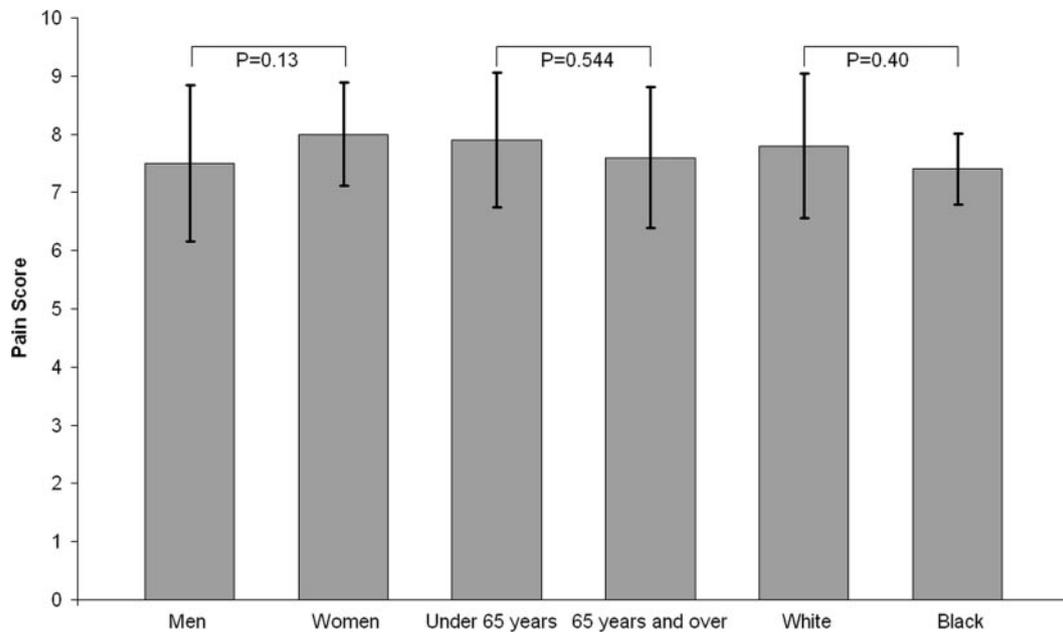


Figure 3. Mean pretreatment pain score by gender, age, and race. Mean pretreatment scores for all groups were in the severe range (7.4 to 8.0). There was no difference in mean pretreatment pain score on the basis of gender, age, or race. The bars depict mean score \pm 1 SD.

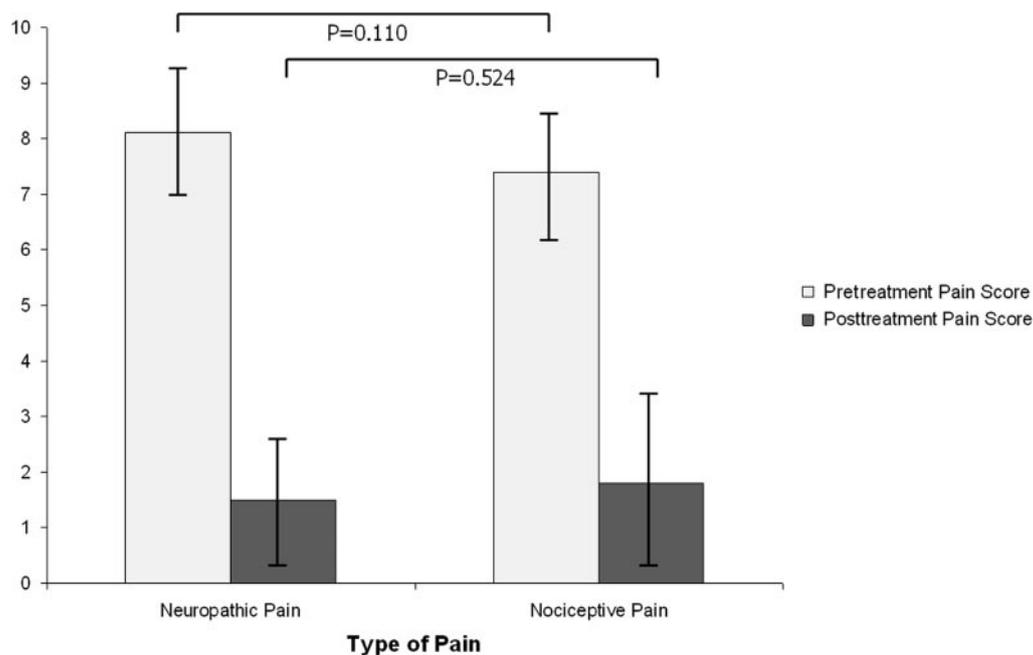


Figure 4. Mean pre- and posttreatment pain scores by type of pain. Mean pretreatment scores for patients who reported neuropathic and nociceptive pain both were in the severe range (8.1 ± 1.2 versus 7.4 ± 1.2 ; $P = 0.11$). There was comparable reduction in pain scores for both groups to the mild range (1.5 ± 1.1 versus 1.8 ± 1.5 , $P = 0.524$). The bars depict mean score \pm 1 SD.

Our finding of the undertreatment of pain in the hemodialysis population has significance for the quality of life of patients with ESRD. Pain may induce depression, anxiety, insomnia, and decreased functional capacity and interfere with the ability to interact socially (2,6,23). An inverse relationship between the

existence of pain and other symptoms and dialysis patients' self-reported quality of life has been reported (2,4).

The SF-MPQ was used in this study. It took only 5 to 10 min to administer, and its use for pain assessment resulted in adequate pain management in 96% of hemodialysis patients. Our

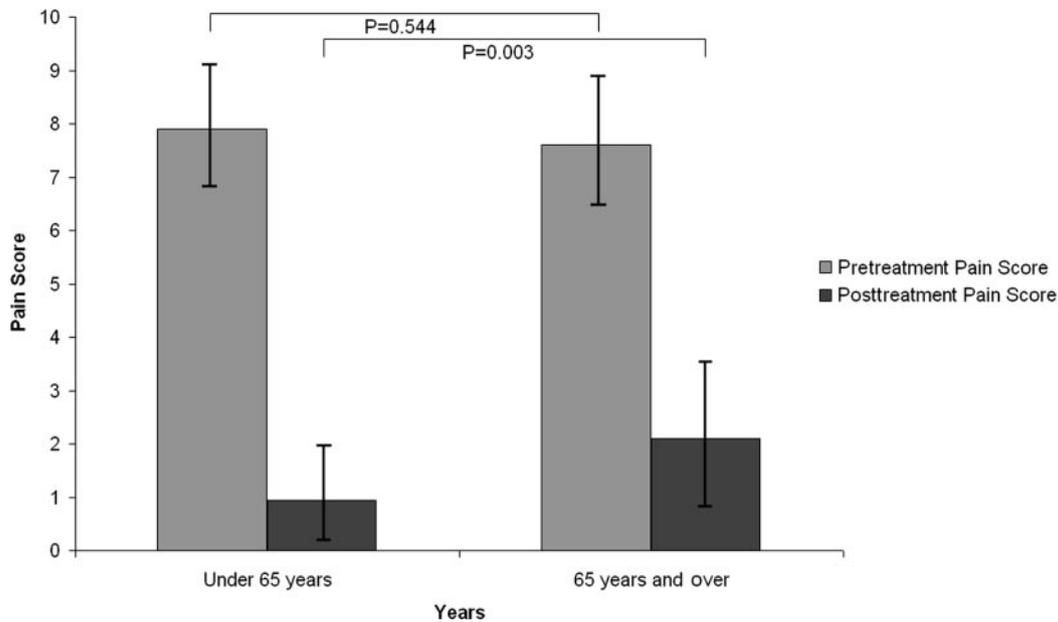


Figure 5. Response to pain treatment by age. Both age groups had reduction of their mean pain scores from the severe to the mild range. Patients who were younger than 65 yr had a significantly lower posttreatment pain score than those who were 65 yr and older (0.94 ± 0.93 versus 2.1 ± 1.4 , $P = 0.003$). The bars depict mean score \pm 1 SD.

patients selected none of the four affective descriptors of pain in the SF-MPQ and only eight of the 11 sensory descriptors. The VAS results were validated by the overall intensity of total pain experience ratings. If our findings are confirmed in other studies of dialysis patients, then it may be possible to construct an even shorter pain assessment form that could be used conveniently once a month in dialysis units.

This study has six limitations. First, the racial distribution of the patients in this study underrepresents minorities because of the homogeneity of the population in West Virginia. Although there was no difference in initial pain rating or response to pain management by race, further studies will be needed to establish the generalizability of our findings. Second, this was a short-term study of only 4 wk; however, the average duration of pain treatment in some of the original WHO validation studies was only 66 to 77 d (24,25). The long-term efficacy of the WHO analgesic ladder approach in ESRD as well as the development of tolerance and adverse effects over time remain to be studied. Third, this study contains a small sample size, but, again, many of the original WHO validation studies had fewer than 100 patients (13). Fourth, this study did not measure formally the impact of the pain reduction on patients' quality of life. Fifth, our population included only hemodialysis patients; a study on the efficacy of using the WHO three-step analgesic ladder in peritoneal dialysis patients remains to be performed. Sixth, our study used the SF-MPQ, the use of which has not been validated in an ESRD population; the use of the longer version, the McGill Pain Questionnaire, has been.

Conclusion

Use of the SF-MPQ for pain assessment and the WHO three-step analgesic ladder approach for pain management in hemo-

dialysis patients led to effective pain relief in 96% of patients. Because older patients had higher posttreatment pain scores and adverse effects from treatment, they will need more careful management to achieve the same results as younger patients. Longer term studies will be needed to confirm these results in a larger, more diverse dialysis population.

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References

1. Davison SN: Pain in hemodialysis patients: Prevalence, cause, severity, and management. *Am J Kidney Dis* 42: 1239–1247, 2003
2. Weisbord SD, Fried LF, Arnold RM, Fine MJ, Leveson DJ, Peterson RA, Switzer GE: Prevalence, severity, importance of physical and emotional symptoms in chronic hemodialysis patients. *J Am Soc Nephrol* 16: 2487–2494, 2005
3. Baile GR, Mason NA, Bragg-Gresham JL, Gillespie BW, Young EW: Analgesic prescription patterns among hemodialysis patients in the DOPPS: Potential for underprescription. *Kidney Int* 65: 2419–2425, 2004
4. Kimmel PL, Emont SL, Newmann JM, Danko H, Moss AH: ESRD patient quality of life: Symptoms, spiritual beliefs, psychosocial factors, and ethnicity. *Am J Kidney Dis* 42: 713–721, 2003
5. Moss AH, Holley JL, Davison SN, Dart RA, Germain MJ, Cohen L, Swartz RD: Core curriculum in nephrology: Palliative care. *Am J Kidney Dis* 43: 1720185, 2004
6. Davison SN, Jhangri GS: The impact of chronic pain on depression, sleep, and the desire to withdrawal from dial-

- ysis in hemodialysis patients. *J Pain Symptom Manage* 30: 465–473, 2005
7. Cohen LM, Germain MJ, Woods AL, Mirot A, Burleson JA: The family perspective of ESRD deaths. *Am J Kidney Dis* 45: 154–161, 2005
 8. Moss AH: Improving end-of-life care for dialysis patients. *Am J Kidney Dis* 45: 209–212, 2005
 9. American Pain Society: *Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain*, 5th Ed., Glenview, IL, American Pain Society, 2003
 10. World Health Organization: *Cancer Pain Relief and Palliative Care: Report of a WHO Expert Committee*, Geneva, World Health Organization, 1990, pp 7–21
 11. Kurella M, Bennett WM, Chertow GM: Analgesia in patients with ESRD: A review of available evidence. *Am J Kidney Dis* 42: 217–228, 2003
 12. Davison SN: Chronic pain in end-stage renal disease. *Adv Chronic Kidney Dis* 12: 326–334, 2005
 13. Melzack R: The Short-Form McGill Pain Questionnaire. *Pain* 30: 191–197, 1987
 14. Grafton KV, Foster NE, Wright CC: Test-retest reliability of the Short-Form McGill Pain Questionnaire: Assessment of intraclass correlation coefficients and limits of agreement in patients with osteoarthritis. *Clin J Pain* 21: 73–82, 2005
 15. Max MB, Portenoy RK: Clinical trials of treatments for pain. In: *Oxford Textbook of Palliative Medicine*, 3rd Ed., edited by Doyle D, Hanks G, Cherny NI, Calman K, Oxford, Oxford University Press, 2004, pp 149–151
 16. Jadad AR, Browman GP: The WHO analgesic ladder for cancer pain management: Stepping up the quality of its evaluation. *JAMA* 274: 1870–1873, 1995
 17. Meldrum M: The ladder and the clock: Cancer pain and public policy at the end of the twentieth century. *J Pain Symptom Manage* 29: 41–54, 2005
 18. Davis MP: Controversies in pharmacotherapy of pain management. *Lancet Oncol* 6: 696–704, 2005
 19. Dean M: Opioids in renal failure and dialysis patients. *J Pain Symptom Manage* 28: 497–504, 2004
 20. American Geriatrics Society Panel on Persistent Pain in Older Persons: The management of persistent pain in older persons. *J Am Geriatr Soc* 50[Suppl 6]: S205–S224, 2002
 21. Module 4: Pain management. In: *The EPEC Project. Education for Physicians on End-of-Life Care*, Chicago, American Medical Association, 1999, pp M4-1–M4-33
 22. Jones KR, Fink RM, Clark L, Hutt E, Vojir CP, Mellis BK: Nursing home resident barriers to effective pain management: Why nursing home residents may not seek pain medication. *J Am Med Dir Assoc* 6: 10–17, 2005
 23. Ingham JM, Portenoy RK: The measurement of pain and other symptoms. In: *Oxford Textbook of Palliative Medicine*, 3rd Ed., edited by Doyle D, Hanks G, Cherny N, Calman K, Oxford, Oxford University Press, 2004, pp 167–184
 24. Ventafridda V, Tamburini M, Caraceni A, de Conno F, Naldi F: A validation study of the WHO method for cancer pain relief. *Cancer* 59: 850–856, 1987
 25. Zech DFJ, Grond S, Lynch J, Hertel D, Lehmann KA: Validation of World Health Organization guidelines for cancer pain relief: A 10-year prospective study. *Pain* 63: 65–76, 1995

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