Reply to K. Jackson et al and W. Leppert

We thank Jackson et al[1] and Leppert[2] for the opportunity to respond to their concerns regarding our article.[3]

Our main point of contention is the belief, on the part of Jackson et al,[1] that unblinded, nonrandomized, prospective audits can give a true indication of the efficacy or toxicity of a drug. Open-label studies do not meet the specific scientific definition of control. The gross underestimation and overestimation of effects in uncontrolled trials, especially studies that involve small numbers of participants, have been well documented.[4] This issue is particularly emphasized by the high placebo response rate (27%) demonstrated in our blinded, randomized controlled trial.

Regarding the issue of patient selection, we suggest that the median average pain scores, opioid equivalent doses at baseline, and selection criteria for resistant pain, despite previous and ongoing treatment with opioids and appropriate coanalgesia, defined the participants in our study as exactly those patients in whom Jackson et al[1] advocate the use of ketamine. The clinical manifestations of participants were consistent with those described as "central sensitization." Moreover, we suggest that the study population was reflective of the type of patient exposed to the drug in everyday clinical practice.

In a series of secondary analyses, we attempted to identify any subset of patient in whom ketamine might have benefit. We were unable to do so. Of interest, during our dissemination program, many clinicians have reported their preference for the use of drug in only patients with predominantly neuropathic pain rather than in patients with predominantly nociceptive pain as is the preference of Jackson et al.[1] This discrepancy emphasizes the lack of any international consensus on the use of this drug.

Another example of variation in practice is in the ketamine dose/toxicity issue. Other authors have suggested that a dose of 500 mg/24 h is excessive and, because of the potential toxicity of delivering this dose over a prolonged period, have chosen to start at a much lower dose.[5] None of these regimens are supported by formal toxicity assessments. We had ethical concerns in continuing the maximum dose for 3 days in the absence of any net clinical benefit. To clarify our study design, all participants with toxicity were given rescue midazolam and/or antipsychotics and offered dose reduction if indicated. Patients were only withdrawn if these measures were unacceptable to the patient or carer. Treating clinicians remained blind to the treatment allocation throughout the study.

We agree that the mechanism of action of ketamine as an N-methyl-D-aspartate antagonist and its role, if any, in central sensitization is postulated and not proven. Perhaps the next best step is to go back to the laboratory and undertake additional preclinical work in an attempt to determine the exact mechanism of any analgesic action of the drug in chronic as well as acute pain. Pain phenotypes have been described that may involve several independent neurobiologic mechanisms.[6] Targeted analgesia may be the way of the future.

We stand by our conclusion that subcutaneous ketamine when used in a dose-escalating regimen over 5 days confers no net clinical benefit at a population level for patients with advanced cancer. Furthermore, we were unable to identify any predictors of response in this cohort. The fact that these patients "have few other options" does not justify the use of a drug that is not only ineffective but also has significant toxicity. Although there is a large body of contrary anecdotal evidence, there is increasing evidence from randomized controlled trials that supports our claim.[7,8]

One of the problems inherent in the current use of ketamine in chronic pain is that there is no standard dose, schedule, or route of delivery. What has become apparent during our international dissemination process is that practice varies widely, ranging from low-dose oral ketamine given on an as-required basis to high-dose parenteral ketamine given as a continuous infusion over 5 days.[5] Many of these schedules are supported by anecdotal reports of dramatic relief from pain,[9] but none of these schedules have been tested formally for efficacy or toxicity in controlled clinical settings.

The regimen chosen for our study was discussed at length and was based on the largest series reported to date in the literature.[10] We agree entirely with Leppert[2] that it is important to "titrate the dose in a careful way." As illustrated in the study diagram (Fig 1), doses in this study were not fixed, and participants did not necessarily escalate to 500 mg over 5 days. Dose escalation and reduction were determined by a combination of both response and toxicity. Patients who showed a beneficial response at 24 hours to either a dose of 100 or 300 mg remained on that dose. Similarly, a dose reduction occurred in the case of failure to respond to rescue medications (antipsychotics and benzodiazepines) and unacceptable toxicity, which was consistent with the clinical assessment of the net clinical benefit.

The high attrition rate inherent in studies of patients with advanced disease is well recognized. The attrition rate of 20% over 5 days seen in our study was anticipated and would have increased significantly if we had used a used a slow titration regimen over a more-prolonged period as suggested by Leppert.[2] Patients with advanced cancer are unwell and often have rapidly progressive disease and an unstable condition. Our dose escalation-reduction regimen over 5 days took these conditions into consideration and rendered our study tenable.

With respect to the level of pain experienced by the participants, although our entry criteria allowed patients with an average pain score ≥ 3, it is clear from Figure 4 in our study that, at baseline, the majority of patients were suffering from at least moderate pain despite previous and ongoing treatment with opioids and coanalgesics. Moreover, the high dose of morphine equivalents recorded at baseline supported our premise that these patients had been taking opiods for some time.

The high incidence of adverse events recorded at baseline (Table 1) may well have been attributable to opioids. The randomization process ensured that the baseline toxicity was evenly distributed between arms. The adverse events reported in Table 3 were those that were scored as being worse than at baseline and were significantly greater in the ketamine arm. To our knowledge, our study is the first to have assessed the extent of ketamine toxicity in a formal prospective manner.

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Research on Chemotherapy-Induced Nausea: Back to the Past for an Unmet Need?

To the Editor: Control of chemotherapy-induced nausea, especially delayed nausea, remains an unmet need.[1] We read with interest the phase III trial by Roscoe et al,[2] and would like to comment on it and respond to the author's discussion of our own work.[3,4]

The article by Roscoe et al[2] is interesting in that it has been accepted without any data on control of vomiting, which is a primary determinant of the risk of delayed nausea (DN).[5,6] It would seem important to know if the control of nausea and vomiting on day 1 was the same in all three comparison groups. Also, one would like to know if the control of vomiting was the same in the delayed phase, for which only data on nausea are presented. We believe that all of the data in the appendix should be reported in the article because these data represent substantial information on the efficacy of the four study arms. In the article, the authors conclude that aprepitant was not more effective than prochlorperazine in controlling DN when both were combined with palonosetron and dexamethasone, but in the Appendix, they "moderate this lack of a statistically significant difference with what might be a clinically relevant benefit for patients receiving aprepitant" (online-only Appendix[2]). Furthermore, the vast majority of patients (95%) received an array of moderately emetogenic chemotherapy regimens, whereas only 5% of patients received highly emetogenic chemotherapy (HEC) containing cisplatin. The power for detecting clinically meaningful differences in average DN severity (primary end point) favoring palonosetron or aprepitant in the HEC setting is therefore weak. To overcome the issue of drugs that have different levels of emetogenicity, a post hoc analysis using data from only patients with breast cancer (54% of the study cohort) receiving doxorubicin-based chemotherapy was performed. Although this unplanned analysis confirmed the overall findings, the case-mix remains a major issue in the interpretation of results. Overall, these questions prevent us from being confident in concluding that palonosetron and granisetron on day 1 carry similar efficacy against DN when prochlorperazine is given on days 2 and 3. The same is true for the observation that when palonosetron was used, aprepitant provided no significant benefit compared with prochlorperazine in preventing DN in patients undergoing HEC or moderately emetogenic chemotherapy.

The absolute difference in DN rates among patients receiving prochlorperazine compared with those receiving a first-generation serotonin antagonist on days 2 and 3 was only 8 percentage points (DN rate from 71% to 79%) in the previous study.[7] In the present study,[2] there was no significant difference in DN rates among patients receiving prochlorperazine compared with those receiving prochlorperazine plus dexamethasone (61% *v* 52%) on days 2 and 3. Likewise, no significant difference in DN rates was observed between the treatment groups receiving either aprepitant plus dexamethasone or prochlorperazine plus dexamethasone (47% *v* 52%) on days 2 and 3. Third, in the group receiving aprepitant, patients experienced less delayed vomiting and also had significantly less DN if vomiting did occur. These data indicate that prochlorperazine may play a specific role in DN when acute emesis is well controlled.

The authors state that more effective regimens against DN should include prolonged dexamethasone, but the benefit of delayed dexamethasone dosing when combined with palonosetron remains an open question. A meta-analysis of individual patient data that we conducted in patients with breast cancer receiving a uniform emetogenic stimulus caused by the combination of an anthracycline plus cyclophosphamide showed that there was no difference in number of nausea-free patients between the treatment groups receiving palonosetron plus 1-day or 3-day dexamethasone during the delayed and overall phases.[8] Also, in the high-risk subgroup of patients age 50 years or younger, there was no difference in the number of nausea-free patients between treatment groups during the 5 days after chemotherapy.

The findings by Roscoe et al[2] may be misleading for readers who are not experts in the chemotherapy-induced nausea and vomiting (CINV) field because they do not really support any departure from

