



HHS Public Access

Author manuscript

Anesthesiology. Author manuscript; available in PMC 2016 May 01.

Published in final edited form as:

Anesthesiology. 2015 May ; 122(5): 967–968. doi:10.1097/ALN.0000000000000638.

Personalized Pain Medicine: Pipe Dream or Reality? Commentary on: The Fibromyalgia Survey Criteria is Associated with Increased Postoperative Opioid Consumption in Women Undergoing Hysterectomy by Janda et al.

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Effective management of both acute and chronic pain using opioids requires finding an appropriate balance between analgesic effects and associated side effects. This balance is generally achieved by dose titration based on actual observed responses to the opioid agent and dose administered. Other than body mass and prior daily use of opioids, there are no well-accepted predictors of opioid responses that can be used to make clinical decisions regarding opioid dosing before opioids are administered. The emerging concept of personalized pain medicine has the goal of using genetic, demographic, and clinical phenotype information available prior to beginning opioid therapy to achieve an optimal balance of analgesia *versus* side effects for a given patient at the time opioid therapy is initiated.¹ At present, high quality replicated research findings in this area remain limited, and there is still no consensus on what predictive factors should be included in personalized pain medicine algorithms. The work by Janda *et al.*² described in this issue is an excellent example of the type of research necessary to make such predictive algorithms a reality.

This well-controlled study evaluated the ability of preoperative fibromyalgia survey scores, a validated self-report measure of widespread pain and other fibromyalgia-related symptoms, to predict postoperative analgesic requirements. Strengths of the study included use of a prospective design, evaluation of a large sample (n=195 patients), inclusion of a comprehensive set of well-validated measures including constructs previously shown to predict opioid responses, and statistical control for potential confounds (such as opioids administered prior to and during surgery). Findings indicated that elevated preoperative fibromyalgia survey scores predicted significantly greater postoperative opioid analgesic requirements, beyond the influence of several other possible opioid response predictors identified in prior literature, including catastrophizing, anxiety, depression, and preoperative opioid use. The magnitude of observed predictive effects appeared to be clinically important, as the postoperative opioid requirements were nearly 29% higher in patients scoring in the upper third of fibromyalgia survey scores compared to those scoring in the bottom third.

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CONFLICTS OF INTEREST: The author has no conflicts of interest.

Although the Janda *et al.* study is a valuable scientific contribution on its own, it is particularly important because it replicates similar prior work. Replication is an extremely important but often overlooked issue in medical research. Its importance is highlighted by reviews in the context of drug development indicating that the majority of published preclinical study results fail to replicate.^{3,4} Replication therefore is necessary before changes in clinical practice can be justified based on research results. Prior work by Brummett and colleagues⁵ using methodology very similar to Janda *et al.* found that in a large total knee and hip arthroplasty sample, each 1 point increase in fibromyalgia survey score predicted an increase in opioid requirements of 9 mg oral morphine equivalents during the postoperative period. Similarly, the current work by Janda *et al.* in women undergoing hysterectomy revealed a 7 mg increase in opioid requirements for each 1 point increase in fibromyalgia survey score. In both cases, these effects were independent of other potential opioid response predictors and confounds, and the similarity in magnitude of effects across two different surgical populations is notable. The replication by Janda *et al.* supports the use of fibromyalgia survey scores in clinical personalized pain medicine algorithms, indicating it is unlikely that these results reflect a spurious significant finding in the absence of any real effect (Type I error). Similarity of results across these two studies also suggests that observed predictive effects are generalizable across genders and surgical populations, potentially justifying use of fibromyalgia survey scores more broadly in clinical decision-making in postoperative pain management.

The findings by Janda *et al.* are also intriguing in terms of mechanisms of pain and analgesia. The authors speculate on possible involvement of endogenous opioid system differences in the observed predictive effects. They cite controlled laboratory work by our group indicating associations between greater endogenous opioid analgesic function and diminished morphine analgesia in the context of both experimental evoked (acute) pain and chronic back pain.^{6,7} Indeed, our prior findings fit a model in which morphine provided less analgesia for those in whom opioid receptor occupancy was already high, a finding also reported in fibromyalgia patients.^{8,9} If confirmed, the current findings by Janda *et al.* suggest that fibromyalgia survey scores might be a clinically practical phenotypic marker for underlying differences in opioid system function that could be used to predict responses to opioid analgesics based on known mechanisms. In contrast, mechanisms by which patient sex and other phenotypic opioid response predictors such as anxiety and depression exert their predictive effects are not currently known.

Future studies in this area would benefit from employing the prospective designs, large samples, comprehensive sets of well-validated measures, and statistical control of confounds used in both the Janda *et al.* and Brummett *et al.*⁵ studies. Whether predictive effects of fibromyalgia survey scores extend to prediction of responses to opioid therapy in the chronic pain context is a clinically-important topic for future research. Little is currently known about any factors that may predict initial or long-term opioid responses in the chronic pain setting.

One methodological limitation of most studies in the area of personalized pain medicine merits highlighting: the outcome measure of opioid requirements. While this outcome is easy to obtain and may indeed reflect differences in analgesic efficacy, it is also possible

that it is a reflection of differences in pain intensity. For example, elevated anxiety, certain genetic variants, and elevated fibromyalgia survey scores may all be associated with differences in neural pain pathways that lead to greater experience of pain post-surgically, and this elevated pain, rather than inherent differences in opioid efficacy, might account for the greater opioid requirements observed in such patients. Although this distinction may be subtle, there might ultimately be different clinical implications depending on whether pain intensity or inherent opioid responsiveness are the source of the observed predictive effects. Future studies should therefore address the possible confounding effects of differing clinical pain intensity on opioid requirement outcomes.

Whether true personalized pain medicine algorithms (in which a set of patient phenotypic and genotypic data can be entered to produce data-based clinical guidance for opioid therapy) will ever be clinically feasible remains to be determined. The supporting data necessary to develop such algorithms is not yet sufficient. Nonetheless, work like the Janda *et al.* study in this issue raise hopes that personalized pain medicine may be more than a pipe dream. At the very least, this study indicates that certain easily assessed phenotypic characteristics can provide useful information to consider when making clinical decisions regarding initial opioid doses in the postoperative setting.

Acknowledgments

FINANCIAL SUPPORT: This work was supported by NIH Grant R01- DA031726. Contents of this work are solely the responsibility of the author and do not necessarily represent official views of the National Institutes of Health.

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