

## Personalised and Precision Pain Medicine—A Dream Coming True?

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In the past 10 years, numerous leaders in pain management have pioneered efforts to raise the awareness of pain medicine. Two notable initiatives included the Decade of Pain Control and Research (2000 – 2010) and the Global Day Against Pain.<sup>1,2</sup> These initiatives have contributed to an increase visibility of pain in daily clinical care settings. All hospitals in Singapore are now accredited by the Joint Commission International and in accordance with the standards exacted, pain is now the fifth vital sign. The “pain load” in an acute tertiary hospital care setting is high. We surveyed 400 inpatients in an audit in 2007 and found the pain prevalence over a 24-hour period to be 51%. More recently, a survey of 736 post elective surgical inpatients revealed that the prevalence of moderate to severe dynamic pain was 53%. When we looked at the data more closely, we were surprised that patients who underwent what we believed were minor surgeries reported more pain than what we had expected. This was consistent with the experience reported by Gerbershagen recently on 50,523 patients from 105 German hospitals.<sup>3</sup> They found that pain scores were often worst in what we considered “minor” procedures such as appendectomy and tonsillectomy. The authors hypothesised that the reasons could be due to less analgesics administered to these patients due to physicians erroneous preconception.

### Mechanism-based Pain Management

Acute pain management should in theory be relatively simple. A predictable surgical injury is induced and depending on the nature and extent of surgery, somato-nociceptive, viscerο-nociceptive or neuropathic mechanisms may predominate. A mechanism-based approach was proposed by Woolf et al in their editorial in 1998.<sup>4</sup> The attractiveness of this model lies in the presumed ability to better target pain management with drugs that act on specific mechanisms. However, it soon became apparent that mechanisms often overlap in clinical pain settings. To a certain extent, the principle of multimodal analgesia in pain management derives from this realisation that

multiple mechanisms and receptors are involved in the transmission of pain. However, despite this approach, acute pain management remains suboptimal.

### Procedure Specific Pain Management

This realisation together with the recent findings by Gerbershagen should strengthen the importance of procedure specific pain management. Different surgical procedures, depending on the nature and extent, induce different degrees of pain and impact the patients’ functionality in different ways. In fact, in the development of these procedure specific pain management guidelines, clinicians are looking beyond pain scores and analgesics consumption. Clinically meaningful outcomes relevant to the specific surgery, such as mobility after a joint replacement and return of bowel function after bowel surgery are recognised to be of equal if not, greater importance.<sup>5</sup> An example of a great resource for such evidence-based procedure specific pain management can be found in websites such as [www.postoppain.org](http://www.postoppain.org).<sup>6</sup> There are limitations to this approach. Firstly, we have yet to develop a comprehensive list of surgical procedures with such evidence-based recommendations. Secondly, any practicing clinician would have witnessed large inter-patient variability in terms of pain intensity reports and analgesic consumption. The problem is predicting which patient will behave in what manner.

### Patient Specific Pain Management

We practise patient specific pain management on a daily basis. We perform preoperative assessments and based on our clinical experience, prescribe perioperative analgesic regimes for our patients. Postoperatively, we assess the patients and decide if the analgesic regimes are adequate and titrate accordingly. However, we do not get it right all the time or sometimes, we take too long to get it right. In the perfect world, patient specific pain management will involve accurate prediction of pain responses to specific operative procedures before surgeries. This, in turn, will

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guide precise pain management strategies for individual patients to achieve timely efficacy with minimal risks. This is the realm of personalised and precision medicine. Such patient specific prediction of postoperative pain may be through genotyping or performance of preoperative pain testing. Both are currently tools used in experimental pain trials.

## Genetics and Pain

The genotype of a patient may influence the pain sensitivity and the analgesic responsiveness through its impact on the pharmacodynamics and pharmacokinetics of drugs. To date, there are more than 300 candidate ‘pain’ genes identified through the use of rodent pain models.<sup>7</sup> Genetic association studies aimed to identify single nucleotide polymorphisms (SNP) in these pain genes encoding receptors, enzymes and ion channels and to use these information to predict analgesic response in individual patients. For example, it was found that the common SNP of the opioid receptor mu-1 (OPRM1) gene, A118G substitution, affect the action of opioids at the receptor. This in turn resulted in differences in pain sensitivity, opioid dose requirements and opioid related adverse effects.<sup>8</sup> However, despite numerous reports of such positive associations, a meta-analysis performed by Walter and Lotsch has failed to show that A118G SNP was consistently associated with certain pain related phenotypes. Similar issues with conflicting data exist for the other SNPs in more than 20 pain genes.<sup>9</sup> The problems besieging these data include design flaws, small sample sizes, inappropriate statistical methods and a lack of awareness of epigenetic mechanisms.<sup>10</sup> Given the current state of affairs, the use of point-of-care genotyping for personalised and precision pain management remains a distant dream.

## Preoperative Pain Test

Quantitative sensory tests are clinical tools used by neurologists to assess and quantify sensory function in patients. It has also been used in experimental settings to evaluate patient’s basal pain perception preoperatively. A recent systematic review of 14 studies by Werner reported that preoperative pain tests may predict 4% to 54% of the variance in postoperative pain.<sup>11</sup> Amongst these studies, different stimulation methods and algorithms were used, including thermal, electrical and mechanical methods. While the predictive strength of these tests was higher than previously reported for single factor analyses using demographics data or psychologic factors, the accompanying editorial cleverly pointed out that we are still no better than the weatherman.<sup>12</sup> The generalisability of the findings of this meta-analysis to all surgeries is also questionable since half the studies were obstetric and gynaecological procedures. Not surprisingly, there was a preponderance of females

in the studies (67%). While gender related comparisons could not be made in this review, there are data showing a higher correlation between responses to experimental pain stimulation and clinical pain in females.<sup>13</sup> Finally, the lack of easy access to these experimental tools and the costs involved mean that routine use of such preoperative pain test is also unlikely for the clinicians in the near future.

## Conclusion

While it may seem that we have reached an impasse, clinicians should remain optimistic that the future for our patients remains bright. The work of our pioneers in pain medicine has created the right milieu for scientists and clinicians to corroborate. Our knowledge of basic pain physiology including pain genetics, has seen unparalleled progress. The growing literature on the use of preoperative pain test may provide the impetus for their use on a more routine clinical basis. Lastly, an increase in awareness by clinicians on the role of procedure specific pain management, including minor surgeries, can lead to better pain relief for our patients. With all stars aligned, our dream of personalised and precision pain medicine may one day come true.

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