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Personalized Medicine and Opioid Analgesic Prescribing for Chronic Pain: Opportunities and Challenges

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Abstract

Use of opioid analgesics for pain management has increased dramatically over the past decade, with corresponding increases in negative sequelae including overdose and death. There is currently no well-validated objective means of accurately identifying patients likely to experience good analgesia with low side effects and abuse risk prior to initiating opioid therapy. This paper discusses the concept of data-based personalized prescribing of opioid analgesics as a means to achieve this goal. Strengths, weaknesses, and potential synergism of traditional randomized placebo-controlled trial (RCT) and practice-based evidence (PBE) methodologies as means to acquire the clinical data necessary to develop validated personalized analgesic prescribing algorithms are overviewed. Several predictive factors that might be incorporated into such algorithms are briefly discussed, including genetic factors, differences in brain structure and function, differences in neurotransmitter pathways, and patient phenotypic variables such as negative affect, sex, and pain sensitivity. Currently available research is insufficient to inform development of quantitative analgesic prescribing algorithms. However, responder subtype analyses made practical by the large numbers of chronic pain patients in proposed collaborative PBE pain registries, in conjunction with follow-up validation RCTs, may eventually permit development of clinically useful analgesic prescribing algorithms.

Perspective—Current research is insufficient to base opioid analgesic prescribing on patient characteristics. Collaborative PBE studies in large, diverse pain patient samples in conjunction with follow-up RCTs may permit development of quantitative analgesic prescribing algorithms which could optimize opioid analgesic effectiveness, and mitigate risks of opioid-related abuse and mortality.

Keywords

Opioid analgesics; chronic pain; personalized medicine; side effects; opioid abuse

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More than 20% of adults may eventually experience chronic pain (CP) [5,6,20,119], with as many as 100 million individuals affected in the United States alone[59]. The past decade has seen dramatically increased use of opioid analgesics for CP management. Extensive population data are emerging that attest to serious safety concerns with opioids, particularly related to high-dose opioid prescribing[80,85]. Not surprisingly, the number of individuals affected by prescription drug abuse has increased, as have rates of opioid-related overdose and death[17,25,29,31,43,48,49,67,68,84,86, 90,91, 101].

Although providing effective analgesia for many, treatment outcomes with opioid analgesics are variable. Long-term opioid therapy may be ineffective or not well tolerated by one-third of CP patients on strong opioids[84]. Successful long-term opioid therapy may be complicated by the tendency for this population to self-select for patients with complex psychosocial comorbidities[32,33,75,104,105,106]. In addition, any analgesic benefits of opioid use must be weighed against related costs, including not only risk for abuse in susceptible individuals[41,64,89], but also negative side effects that include constipation, nausea, sedation, respiratory depression, and death[31,84]. The possibility of opioid-induced hyperalgesia[7,30] and potentially deleterious alterations in brain function and structure[113,125] must also be considered. These latter changes may contribute to “abnormal behaviors” noted to occur in some individuals during the course of chronic opioid therapy. Recent evidence further

indicates that patients who remain on opioids tend to dose escalate, sometimes dramatically, creating a potential conundrum as clinicians pursue an ever-moving target for adequate pain relief[75,79,97].

At present, there are no well-validated means of identifying optimal candidates for chronic opioid therapy[29,109]; that is, individuals who will experience good analgesic effectiveness at stable dosages with limited side effects and low risk of abuse. A critical research question therefore is what phenotypic and genotypic profiles characterize patients for whom the cost/benefit ratio of chronic opioid therapy is favorable versus unfavorable. Specifically, how can patients be identified before initiating opioid therapy who are more likely to enter an unfortunate spiral into unsafe dosing that they believe is preferable to living without opioids, even though they may find no dosage is ever adequate?

Is Personalized Medicine A Solution?

The concept of "personalized medicine," optimizing medication types and dosages for individual patients based upon genetic, biomarker, and other patient-related factors, has received increasing attention[47,71]. Its application to the field of pain management is tantalizing in theory, but is, as yet, unrealized in practice. The necessary research base to support a true personalized medicine approach to opioid analgesic prescribing is still several years away. This paper will provide an overview of key issues regarding research strategies for building the database necessary to develop and validate personalized analgesic prescribing protocols. Several genotypic and phenotypic factors that could potentially serve as predictors of opioid responses within a personalized analgesic prescribing protocol will be briefly discussed. Given space limitations, this paper will focus specifically on opioid analgesic prescribing for chronic, non-cancer pain, although many similar issues may apply to personalized prescribing of other classes of pain therapeutic agents (e.g., anticonvulsants).

Research Strategies to Develop Personalized Analgesic Prescribing Protocols

Traditional prospective, randomized, placebo-controlled trials (RCTs) are the gold standard for demonstrating analgesic efficacy with the fewest challenges to internal validity[26]. They are optimized to demonstrate analgesic efficacy at the group level (i.e., mean analgesic response in active treatment versus placebo condition) in patients with a specific CP diagnosis. Typically, trial participants have been highly selected to maximize homogeneity and reduce confounds that might weaken clinical effects. While the strict sample selection criteria, protocol standardization, and controlled nature of RCTs are ideal for conclusively demonstrating analgesic efficacy in the "average patient," they are less than ideal for addressing the complex clinical questions at the core of personalized analgesic prescribing. That is, what profile of individual difference factors predicts optimal analgesia with the lowest abuse risk and fewest negative side effects over the long-term?

A key limitation with standard RCT protocols is the sample size required for adequate statistical power to permit responder subgroup analysis, something for which RCTs are not usually designed. For example, examining the impact on opioid responses of a single dichotomous individual difference factor with a moderate effect size might require only two groups with 30 patients each in a traditional crossover RCT design. However, assuming a similar effect size, studying the impact of only three dichotomous predictors simultaneously in a fully factorial RCT design would require 240 patients (8 possible combinations × 30 per group). Thus, testing of increasingly large combinations of individual difference variables within the RCT framework requires dramatic increases in sample size that can quickly become pragmatically unfeasible. Due to their expense, RCTs are also typically of relatively short duration[27], creating potential generalizability issues given the frequent long-term nature of clinical opioid therapy. Indeed, clinical experience suggests that long-term opioid

use can produce adaptations that alter not only efficacy, but also some patients' ability to rationally report effectiveness. Pragmatic limitations of RCTs related to sample homogeneity, sample size requirements, and duration of therapy all point to the challenges of exclusive reliance upon RCTs to build the database from which personalized analgesic prescribing protocols can be developed.

As a complement to traditional RCTs and mechanistically-focused laboratory research, studies using systematic practice-based evidence (PBE) approaches may also be useful. PBE is a prospective observational cohort study design that can be used to discern the relative contribution of specific interventions (individually and in combination) to patient outcomes while taking into account the impact of relevant individual difference variables[57]. As a non-randomized, non-placebo controlled design, ability to infer causality in PBE studies is more limited than with RCT studies. However, the PBE study design is well-suited to address some of the limitations of RCTs. PBEs can include highly diverse clinical patients, potentially in large numbers, who vary on multiple individual difference variables that may be relevant to personalized analgesic prescribing. Analyses of these datasets thus may permit examination (albeit in a less than conclusive way) of the impact of complex patient profiles on analgesic responses.

Unlike RCTs, the PBE model incorporates research data capture as part of clinical pain management. Both patients and providers record standardized data elements as part of routine care. This approach permits efficient data capture in very large and diverse samples with standardized long-term outcomes, all of which are difficult to achieve efficiently within the traditional RCT model. Data obtained may include medical and psychiatric diagnoses and comorbidities, clinical presentation (signs and symptoms, brain imaging findings), illness severity, medications and dosages, side effects, abuse-relevant red flags (e.g., early opioid refills), other interventions (e.g., complementary and alternative medicine therapies), genetic variables, and validated pain, psychosocial, and functional outcome measures recorded in electronic databases. Several computerized systems for comprehensive patient self-reported outcomes are already in development or in use[39,94], including computerized adaptive testing systems such as the NIH PROMIS measures (www.nihpromis.org). Within the PBE approach, electronic medical record data can be combined with computer-based patient-reported outcomes to rapidly identify those CP patient phenotypic and genotypic characteristics that may be associated with favorable treatment outcomes, although with less certainty than with RCTs[1,2,3,37,38]. Systematic large-scale PBE studies may help accrue the data necessary to generate hypotheses that would support development and subsequent validation via traditional RCTs of evidence-based personalized analgesic prescribing protocols. While having several advantages, results of multisite PBE studies will be influenced by the greater variability in the interventions being employed compared to standardized RCTs, reflecting the diverse treatment styles of participating PBE study providers. Moreover, PBE study results will generalize only to the populations included in such studies, underscoring the importance of seeking participation from diverse clinical sources (e.g., traditional chronic pain clinics, oncology clinics, geriatric populations, etc.).

The PBE model is currently being employed in a collaborative Chronic Pain Registry at Weill Cornell Medical College, the Memorial Sloan Kettering Cancer Center, and the Hospital for Special Surgery in New York City[95]. Evidence-based personalized analgesic prescribing could be realized more rapidly through expansion of such PBE efforts into a Nationwide Chronic Pain Patient Registry using a standardized clinical assessment and imaging approach, including collection of samples for genotyping. By standardizing protocols across a large number of sites, such protocols can provide for common phenotypic characterization of patients and collection of a common set of potential biomarkers and other predictors in large numbers of patients. Large-scale coordinated PBE efforts of this type

may make it possible within the next few years to accrue sufficient numbers of CP patients with the diverse phenotypic and genotypic characteristics necessary to permit development of quantitatively-derived treatment algorithms.

The optimal statistical methodology for determining the relative contributions of individual profile elements to treatment outcome (which may be many and small), as well as methods to verify independent cohort replication, will need to be formally established and validated in order to reduce the false positive and negative correlations that may confound results with any intensive longitudinal design. The sample sizes necessary to reliably detect significant associations will also need to be determined. Experience indicates the likely need for very large patient cohorts with matched controls to provide the very low probability values ($<10^{-8}$) required to provide "genome wide significance" in standard genome wide association studies. Nonetheless, early data regarding the PBE approach are promising. For example, a PBE cohort of 1,100 patients was able to identify a strong association between opioid use and better stroke rehabilitation outcomes[55,57]. One promising statistical methodology for determining personalized prescribing algorithms is an actuarially-based approach, similar to that used to develop insurance risk tables. This methodology could provide a quantitative probability of successful opioid therapy given an *a priori* profile of key patient characteristics.

Even prior to availability of personalized prescribing algorithms, individual patients may benefit immediately from the monitoring of standardized clinical outcomes that are acquired routinely in PBE protocols, thereby facilitating "metric-based pain care." That is, standardized quantitative outcomes can be used to systematically monitor treatment responses and provide rapid feedback to guide decision-making regarding analgesic regimens and dosing.

Although very different in design, findings from RCTs and PBEs may prove complementary. Following RCTs that identify improved analgesic agents with known efficacy in the "average patient," subsequent monitoring with large-scale PBE registries can be used to identify individual difference characteristics that may moderate outcomes with these agents. These PBE Chronic Pain Registry data might, for example, suggest that a particular combination of genetic and biomarker variables predicts a much more favorable cost-benefit ratio for a given opioid analgesic in a certain CP diagnostic group. The successful development of personalized opioid prescribing protocols would therefore benefit from a sequential approach, first by establishing broad coordinated PBE pain registries that can pool their data to identify candidate predictors of opioid analgesic responses, with these less controlled studies followed-up by more rigorous RCTs to validate the predictive utility of these candidates.

PBE data resulting from large coordinated pain registries can also be used to inform preclinical development of new analgesic drug targets (i.e., reverse translation), and to facilitate enriched patient selection for more traditional RCTs. Hybrid study designs that obtain controlled laboratory experimental data on subsets of CP patients who are simultaneously participating in prospective clinical PBE studies may also prove useful. For example, obtaining brain imaging, quantitative sensory testing, metabolomic, proteomic, and epigenetic data that objectify analgesic outcomes in a subset of PBE pain registry patients could help validate treatment-related changes observed in more subjective traditional pain outcomes (see below), and potentially increase confidence in these PBE results despite their inherently less controlled nature.

One barrier to large-scale coordinated PBE efforts is potential bias against non-RCT trial designs on the part of funding sources and scientific review panels. Such bias no doubt is

related to the fact that PBE designs suffer from threats to internal validity that traditional RCTs do not[26], and thus provide less conclusive results. RCTs to demonstrate efficacy convincingly and highly-controlled laboratory studies to clarify mechanisms of pain and analgesia will always be necessary, but complementary funding for design and coordination of large-scale PBE clinical registries will help provide the diversity of individual difference information necessary for the goal of evidence-based personalized analgesic prescribing to be realized. Several potential predictors of opioid analgesic responses that might be incorporated in personalized medicine algorithms are now briefly discussed.

Genetic Variability

Substantial evidence, primarily using classical and molecular genetic approaches, document heritable influences on individual differences in vulnerability to dependence on opioid analgesics[107]. Similar genetic approaches provide more modest evidence from human studies, and stronger evidence from animal studies, that support heritable differences in perception of pain, degree of analgesia in response to opioids, and/or development of tolerance and physical dependence on opioid analgesics[9,70]. Genome wide association studies (GWAS) are required to identify optimal genetic inputs into personalized analgesic prescribing algorithms but, to date, such studies have not been robust[54]. Beyond the influences of genetic differences per se, future work may also need to consider the impact on opioid analgesic responses of individual differences in genetic transcription, mRNA editing, and protein translation.

There are likely to be common polygenic, and not major gene, effects on vulnerability to opiate dependence, based on a convergence of linkage and GWAS data from individuals who are often dependent on multiple substances with addictive potential including opioid analgesics. Limited human data confirm that both opioid analgesic efficacy and risk for opioid abuse are also likely subject to polygenic influences[58,73,82,126]. Ability to quit smoking provides a parallel clinical example of a similar underlying genetic architecture. A weighted, complex genetic score based on 12,000 single nucleotide polymorphisms (SNPs) predicted clinical smoking cessation outcomes as well as any other clinical predictor (area under ROC curve almost 0.7)[110]. It is likely that similar genetic scores will eventually improve our ability to identify individuals at genetically-increased risk for enhanced abuse liability when undergoing opioid analgesic therapy, and more generally, improve identification of patients likely to have a favorable risk/benefit profile prior to initiating opioid therapy.

Although these findings are clinically intriguing, genetic data necessary for developing personalized analgesic prescribing protocols are currently lacking. Achieving this goal will require GWAS studies of individuals with carefully selected phenotypes regarding pain, analgesic responses (acute and chronic), hyperalgesia, tolerance and physical dependence, craving, and other addiction-related factors. These efforts will also need to elucidate pharmacogenomic influences, both drug-specific and those common across opioid analgesic agents, on drug pharmacokinetics and pharmacodynamics. Such data will help match pain patients with the specific opioid agent and doses likely to provide the most effective analgesia with the fewest side effects. An example of drug-specific influences is the high degree of polymorphism in the CYP2D6 gene whereby multiple SNPs or even duplication of this gene can significantly alter metabolism and analgesic responses to codeine[36]. Examples of genetic influences that may be common across different opioid analgesics are findings that the A118G single nucleotide polymorphism (SNP) of the mu opioid receptor gene and the V158M SNP of the catechol-o-methyltransferase gene may alter both analgesic responsiveness and opioid abuse risk[45,52,65,69,100,126,127]. Although the A118G SNP is

probably the most widely investigated single genetic variant in this context, its degree of impact on opioid analgesic responses remains debatable[117].

Chronic Pain Mechanisms

The phenotypic expression of CP reflected in its signs and symptoms is often the result of multiple interacting mechanisms, both peripheral and central, and these might impact on opioid analgesic responses. In the case of neuropathic pain, underlying mechanisms may include sensory damage (leading to negative symptoms such as decreased pain sensitivity), peripheral sensitization (increased pain sensitivity), central sensitization (allodynia), ectopic activity (spontaneous pain), and localized immune activation[114]. Statistical methods can distinguish distinct somatosensory profiles of neuropathic CP, reflecting different combinations of underlying mechanisms[16,98]. Potential relevance of sign/symptom profiles to personalized analgesic prescribing is suggested by work revealing greater opioid analgesic efficacy in neuropathic CP patients displaying signs of hypoalgesia to acute pain[34]. A recent open-label study further suggests that responses to a novel opioid analgesic (prolonged-release tapentadol) in chronic low back pain patients is positively correlated with the extent to which neuropathic pain signs are reported[103]. These limited findings suggest that data on contributory CP mechanisms, as reflected in clinical characteristics and test results, may be a useful element of personalized analgesic prescribing algorithms.

Brain and Neurotransmitter Function Biomarkers

Emerging evidence suggests that personalized analgesic prescribing algorithms may also need to address brain and neurotransmitter changes associated with CP. Recent work reveals that patterns of brain connectivity can identify patients who will transition from acute to chronic pain, hinting that development of chronic pain may be linked with altered brain function[14]. A series of brain imaging studies further suggests that diverse chronic pain conditions, including chronic low back pain, complex regional pain syndrome, osteoarthritis, post-herpetic neuralgia, and chronic pelvic pain, each may activate distinct brain networks and be associated with reproducible patterns of brain reorganization[10]. Radiotracer imaging studies in healthy individuals indicate that analgesia in response to opioids is linked to selective activations in specific brain regions rich in opioid receptors[93,115,116]. One might therefore expect the pattern of brain changes unique to each CP condition, if they affect brain regions that are opioid responsive or that modulate opioid function, to be associated with differential responsiveness to opioid analgesics. In this case, different CP diagnostic categories might be associated with differential opioid responsiveness via their associations with different patterns of underlying brain changes. This latter possibility remains to be adequately tested, but existing data are intriguing. Consistent with this hypothesis, PET imaging studies suggest that different pain conditions (inflammatory, neuropathic, fibromyalgia, cluster headache) may indeed differ in their patterns of central opioid receptor availability[50,51,53,61,62,63,74,102,122]. These differences in opioid receptor availability in turn would likely influence responses to opioid analgesics[40].

Dopaminergic neurotransmitter systems also have been shown to be involved in the central processing of pain signals[99,124]. Alterations in dopaminergic function have been described in persistent pain conditions such as chronic low back pain and fibromyalgia[13,123,124], as well as in opioid dependence[46], suggesting potentially important commonalities in neurotransmitter pathways that may impact on personalized opioid prescribing. Potentially synergistic interactions between neurotransmitter pathways are highlighted by findings that degree of analgesia in response to opioids may be modulated by dopaminergic function[66]. Understanding the inter-individual variations in brain and neurotransmitter system function may then be critical for development of personalized medicine algorithms for opioid

analgesic therapy. Although more studies are needed, one possibility is that brain imaging might be used in clinical treatment planning if opioid analgesic therapy is to be considered. Identifying more clinically accessible means of characterizing neurotransmitter biomarkers also represents an important topic for future research.

Other Patient Characteristics

Some evidence suggests that male gender[83], elevated negative affect[60,87,88,118], elevated sensitivity to laboratory acute pain stimuli[34,35], lower temporal summation[35], and elevated endogenous opioid levels[92] might be associated with reduced responsiveness to opioid analgesics. Synergistic interactions between opioid analgesic medications and greater endogenous pain inhibitory function have also been noted, potentially of relevance to tailoring of opioid analgesic dosing[11,28,121]. Whether the influence of these diverse factors on opioid analgesic responses might be explained in part by any common mechanism is not known. However, some literature suggests that underlying differences in endogenous opioid systems related to these factors could contribute[22,23,24,42,44,120]. Possible utility of these patient characteristics to serve as biomarkers for relevant neurotransmitter, brain, or other biologic differences influencing opioid analgesic responses remains to be explored.

Patient status regarding comorbid medical conditions that could alter opioid metabolism (e.g., renal impairment) and potential drug-drug interactions that could produce problematic side effects also need to be considered[108]. This may be particularly important among the elderly, in whom there is a higher likelihood of multiple comorbid medical conditions and polypharmacy[4,108].

Potential for Treatment Synergism

There are hints that personalized analgesic prescribing algorithms may need to incorporate information regarding other treatments, due to potential for synergistic effects with opioid analgesics. Several non-pharmacological pain management approaches including acupuncture, relaxation training, and aerobic exercise may activate opioid pathways, which in theory might alter opioid analgesic responses[76,77,51]. Individual differences in placebo response may also be associated with differences in opioid system activity that could influence analgesic responsiveness. Acupuncture provides an instructive example. Both real and non-insertive sham (placebo) acupuncture have been shown to reduce clinical pain in fibromyalgia patients via opioid-related mechanisms[51]. Sham acupuncture reduced mu-opioid receptor (MOR) binding availability in a manner consistent with enhanced release of endogenous opioids, a proposed placebo mechanism[128]; however, real acupuncture *increased* MOR binding availability within the same brain regions[51]. One interpretation of these data is that real acupuncture may have resulted in an up-regulation in MOR number and/or binding affinity, a change that would be expected to directly enhance responses to opioid analgesic medications. If confirmed in controlled trials, synergism between non-pharmacological treatments and opioid analgesic responses might permit reduced opioid dosages, potentially reducing side effects, tolerance, and possibly abuse risk[72]. Similar issues with synergism between opioid analgesics and non-opioid pharmacologic treatments (e.g., antidepressants, alpha-2 adrenergic agonists)[15,78] also will need to be addressed in personalized medicine algorithms.

Outcome Measures and Development of Personalized Analgesic Protocols

A key question in developing personalized analgesic prescribing protocols is how to define “adequate analgesia.” The most common primary pain outcomes in analgesic trials are subjective pain ratings. While valid in the psychometric sense, patients’ perceptions and reports of what constitutes adequate therapeutic efficacy may not correspond well with what

the clinician would consider successful and may be unrealistic[85,96]. The magnitude of clinical pain complaints (pain ratings, pain behavior) may also be inconsistent with the underlying pathological condition, underscoring how traditional subjective clinical outcomes for determining opioid analgesic efficacy may be influenced by multiple non-nociceptive psychosocial factors (e.g., litigation, reinforcement contingencies).

One potential way to increase the objectivity of pain outcomes in studies aimed at developing personalized analgesic prescribing algorithms is use of brain imaging technology[18,19]. Recent fMRI work demonstrates that the opioid analgesic buprenorphine reduces functional connectivity in sensorimotor and sensory-discriminative brain circuitry in a dose-dependent manner[111]. Altered functional connectivity can also discriminate between effective and ineffective opioid analgesics[112]. Other studies in chronic back pain and fibromyalgia patients suggest that activity within specific brain regions or brain connectivity between regions may track chronic back pain intensity reliably[12,80]. Finally, fMRI work using support vector machine learning to examine whole brain activity patterns suggests that brain imaging can objectively detect individual differences in pain experience[21]. Each of these findings points toward the potential for brain imaging techniques to serve as objective measures of analgesic response for use in research, including the hybrid PBE/laboratory studies noted above.

The importance of addressing the impact of opioid analgesics not only on analgesic markers but also on functional measures (both patient-reported and objectively assessed) should also be noted. Such issues may be particularly relevant when opioids are being considered for pain management among individuals with limited ability to communicate (e.g., advanced Alzheimer's disease).

Conclusions

Opioid analgesics are increasingly used for chronic pain management. Due to side effects and abuse potential, their costs/benefits must be weighed carefully. While a personalized medicine approach to opioid analgesic prescribing is highly desirable, at present there are insufficient data for deriving quantitative algorithms to achieve this goal based on individual patient phenotypes or genotypes. Nonetheless, available studies have identified a number of potential predictors of analgesic responses that merit further evaluation. RCTs remain the gold standard for conclusively demonstrating analgesic efficacy. However, development of personalized medicine algorithms for opioid analgesic prescribing within the next few years will likely require concomitant studies using non-randomized PBE designs for phenotyping and genotyping that permit acquisition of large and diverse samples with long-term follow-up data more reflective of real world clinical pain therapy. Subsamples of PBE participants ideally would also participate in more controlled laboratory studies (e.g., brain imaging, quantitative sensory testing) that may enhance interpretation of PBE outcomes. RCTs will always provide basic efficacy data to inform PBE studies. Following these initial studies, a sequential research approach in which candidate predictors are identified based on multisite PBE registries, followed by subsequent validation of these predictors in more rigorous and conclusive RCTs will likely provide the most cost-effective and rapid path towards true evidence-based personalized analgesic prescribing algorithms. Although beyond the scope of this paper, other opioid prescribing issues will still need to be addressed once effective prescribing algorithms are validated. For example, how should patients be informed that they are not good opioid candidates, what alternatives should be selected and how, and how should patients who demonstrate a poor opioid cost/benefit ratio despite optimal algorithmic selection best be managed? Personalized analgesic prescribing has enormous potential to benefit patients by enhancing real world clinical care and optimizing the cost/benefit ratio of opioid analgesic therapy.

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