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A proposed protocol for personalised prediction of opioid response in oncology patients with chronic pain using machine learning methods combining genetic and clinical factors

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ABSTRACT

Opioids are a cornerstone treatment for chronic pain in oncology patients, yet individual response varies widely due to genetic differences in CYP2D6 enzyme activity, which governs the metabolism of codeine and tramadol. Patients are classified into four metaboliser phenotypes, each associated with distinct efficacy and side-effect profiles. The current study proposes a research protocol integrating genetic and clinical data through machine learning models (WEKA, Omics-CNN) to predict individual opioid response. Patients from the Hippocration Pain Unit will undergo CYP2D6 genotyping and standardized pain assessment. The aim is to develop a predictive tool to support personalised, evidence-based opioid prescribing in cancer pain management.

Key Words: *Opioid response; chronic cancer pain; machine learning; CYP2D6 enzyme*

INTRODUCTION

Opioids play a crucial role in managing chronic pain among cancer patients. Their pain-relieving effects stem from their action on μ-opioid receptors, which are encoded by the OPRM1 gene [1]. The hepatic metabolism via the cytochrome P450 (CYP450) enzyme activates the analgesic action of opioids like codeine and tramadol [4]. However, patients differ in their metabolism of analgesics. Genetic differences in CYP450 enzymes impact how a patient responds to medications, influencing both their effectiveness and the risk of side effects like nausea, constipation, or even respiratory issues [2]. The genetic variations, in combination with clinical factors, result in a wide range of responses to opioid therapy. Based on these genetic variations, patients are classified into four metaboliser phenotypes: ultrarapid, extensive (normal), intermediate, and poor [4,5]. The key characteristics of each group are summarised in Table 1.

The high complexity of genetic variations and their interactions with clinical factors presents challenges in predicting individual responses to opioid therapy. Machine Learning algorithms can integrate large, heterogeneous datasets and analyze both the role of individual variables and their interactions in shaping the outcome.

In current literature it has been examined the genetic effects in opioid response. Although, the CYP2D6 plays a crucial role in opioid metabolisation of tramadol and codeine, does not explain alone the full heterogeneity of opioid response. Polymorphisms in other genes, such as ABCB1, COMT, OPRM1 have been implicated in opioid metabolism in patients.

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TABLE 1. Metaboliser phenotypes groups.

Metaboliser phenotype	Characteristics
Ultrarapid Metaboliser	These individuals express multiple functional copies of the CYP2D6 gene, leading to accelerated drug metabolism. The hypermetabolism may lead to reduced drug efficacy due to rapid metabolism and thus the need for higher doses to achieve therapeutic levels, posing a risk of toxicity.
Extensive (Normal) Metaboliser	Extensive Metabolisers typically have functional alleles that facilitate efficient drug metabolism. However, variability within this group can affect drug response and may require individualised therapeutic approaches.
Intermediate Metaboliser	These metabolisers possess alleles that confer intermediate enzymatic activity, resulting in a metabolic rate between that of Poor Metabolisers and Extensive Metabolisers. Intermediate Metabolisers may require dose adjustments or closer monitoring to ensure optimal therapeutic results.
Poor Metaboliser	Individuals with minimal or no CYP2D6 enzyme function due to homozygous or compound heterozygous inheritance of non-functional alleles. Individuals in this category may exhibit reduced metabolic rates, leading to increased drug exposure and increased risk of adverse reactions.

There is limited research, applying machine learning techniques to the analysis of opioid response specifically in chronic cancer pain populations. Previous studies have either focused solely in the role of demographic and clinical data in opioid response or have drawn insufficient conclusions regarding different genetic factors. There is currently a lack of integration of machine learning approaches into predicting patient response to opioids.

The present study aims to address this gap in the literature by analysing both genetic and clinical data, examining their individual and combined contributions to patients' responses to opioid therapy. This study presents a proposed research protocol. Patient recruitment and data collection are underway.

Protocol and Implementation

This study sets out to build a machine learning model that can predict how individual patients will respond to opioids by analysing both their genetic makeup and clinical data. The study will include patients who are monitored in the Hippocration Pain Unit, suffering from chronic pain of benign or malignant aetiology and requiring treatment with weak opioids (codeine or tramadol). Patients with proven contraindication to the administration of paracetamol, codeine or tramadol, serious psychiatric or neurological disease under treatment, history of epilepsy or craniocerebral injury, serious cardiac-renal-hepatic insufficiency under treatment, severe chronic obstructive pulmonary disease, severe sleep apnoea, history of allergic reaction to the administered substances, history of substance and alcohol abuse, pregnancy/lactation, age <18 years and patient refusal will be excluded.

During the initial visit, a comprehensive medical and pain history will be obtained, including concomitant medications and baseline pain intensity, and a blood sample will be collected. To standardise data collection, a predefined questionnaire has been developed to ensure consistent medical history for all participants. Pain intensity will be evaluated through close follow-up, by using the Numeric Rating Scale (NRS 0-10) as well as the Brief Pain Inventory (Greek version). The reassessment of pain intensity and the patient's response to analgesics will be done after 72 hours, where the percentage of pain relief and all adverse effects from the use of the medications will be recorded, with a positive or negative answer in specific questions. The pain level after the therapy and the adverse effects will be documented in the initial patients' record. If in the follow-up, the pain levels are NRS <4 or at least a 50% reduction in pain intensity, this will be considered a positive drug response. Codeine and tramadol will be administrated randomly, in a titrated dosage, depending on the age and co-existing diseases of each patient. Specific dosage ranges and increments will be defined in the finalised protocol. Blood samples, will be stored refrigerated at -20° C until analysis. For analysis, genetic material will be isolated from 2 ml of peripheral blood of each participant and will be applied either Real-time PCR (Polymerase Chain Reaction) or PCR-RFLP (Restriction Fragment Length Polymorphism) for the 16 for the 16 clinically significant polymorphisms of the CYP2D6 gene *1XN, *2, 2A, *3, *4, *5, *6, *7, *8, *9, *10, *12, *14, *17, *29, *41[6].

A sufficient sample size is required in order to draw meaningful conclusions. The aim is to recruit 50 patients per group. After collecting the genetic data, an anonymised Excel spreadsheet will be created to combine all genetic and clinical data for each participant, along with their treatment response. In the final stage

of the analysis, a detailed, high-dimensional model, integrating genetic and clinical data, will be developed, tailored to forecast responses specifically to tramadol and codeine in cancer patients. In order to determine the optimal predictive model, multiple experiments will be performed using different machine learning and deep learning approaches.

All algorithmic approaches will be conducted using the WEKA software, ensuring standardised implementation and reproducibility of results. Furthermore, the study will assess the effectiveness of a tailored Convolutional Neural Network for analysing genetic data (Omics-CNN) [7]. In the initial stages, the Local Outlier Factor method and Principal Components Analysis (PCA) will be applied to identify potential outliers.

Algorithms performance will be reviewed based on discrimination (AUC), overall accuracy, and calibration of predicted probabilities. In the initial analyses, all individual features from each sample will be treated equally, with no predefined weighting on their impact on the final outcome.

Following model training, t-tests and the Minimum Redundancy–Maximum Relevance (mRMR) [7] method will be applied to assess the contribution of individual variables, as well as their combined interactions, in shaping the final predictions. The computational model is expected to provide predictions and useful knowledge, leading to more tailored pain management strategies.

The predictive framework will be used as basis for the creation of an API tool for clinical use in personalised opioid prescribing.

CONCLUSION

The protocol introduces an innovative approach to **opioid** therapy in chronic cancer pain management by integrating machine learning into clinical practice, by combining genetic and clinical data so as to minimise **opioid**-related side effects and support a more personalised approach to patient therapy. The use of such a tool can help identify patients who are likely to respond positively to tramadol or codeine and those at higher risk for adverse effects. Tailoring treatment based on genetic profiles may reduce trial-and-error prescribing, enhance positive outcomes, reduce the risk of adverse effects, and optimise analgesic efficacy.

This study can be expanded to either integrate data of patients under multimodal analgesia, or to examine the role of other genetic factors in **opioid** response. From this perspective, valuable insights could be gained regarding the combined effects of multiple genetic variants. The high performance of deep learning models stems from their ability to generalise effectively to new data. This is why there is a strong demand for integrating large and diverse datasets into these algorithms. However, the high cost of blood analysis, poses significant challenges in expanding by increasing the sample size. To overcome the challenge posed by the high cost of collecting genetic data, model performance will additionally be assessed using open-access genetic datasets, so as to evaluate the generalisability of the algorithm. Ongoing validation and refinement will enhance the model for future clinical application, ultimately improving the quality of life for oncology patients.

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