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Published in:
BMJ Open

DOI:
10.1136/bmjopen-2014-006818

Published: 2015-01-01

Citation for published version (APA):

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Can variability in the effect of opioids on refractory breathlessness be explained by genetic factors?

David C Currow,1,2 Stephen Quinn,3 Magnus Ekstrom,1,4 Stein Kaasa,5,6 Miriam J Johnson,7 Andrew A Somogyi,8 Pål Klepstad9,10

**ABSTRACT**

**Objectives:** Opioids modulate the perception of breathlessness with a considerable variation in response, with poor correlation between the required opioid dose and symptom severity. The objective of this hypothesis-generating, secondary analysis was to identify candidate single nucleotide polymorphisms (SNP) from those associated with opioid receptors, signalling or pain modulation to identify any related to intensity of breathlessness while on opioids. This can help to inform prospective studies and potentially lead to better tailoring of opioid therapy for refractory breathlessness.

**Setting:** 17 hospice/palliative care services (tertiary services) in 11 European countries.

**Participants:** 2294 people over 18 years of age on regular opioids for pain related to cancer or its treatment.

**Primary outcome measures:** The relationship between morphine dose, breathlessness intensity (European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire; EORTC-LOC30 question 8) and 112 candidate SNPs from 25 genes (n=588).

**Secondary outcome measures:** The same measures for people on oxycodone (n=402) or fentanyl (n=429).

**Results:** SNPs not in Hardy-Weinberg equilibrium or with allele frequencies (<5%) were removed. Univariate associations between each SNP and breathlessness intensity were determined with Benjamini-Hochberg false discovery rate set at 20%. Multivariable ordinal logistic regression, clustering over country and adjusting for available confounders, was conducted with remaining SNPs. For univariate morphine associations, 1 variant on the 5-hydroxytryptamine type 3B (HTR3B) gene, and 4 on the β-2-arrrestin gene (ARRB2) were associated with more intense breathlessness. 1 SNP remained significant in the multivariable model: people with rs7103572 SNP (HTR3B gene; present in 8.4% of the population) were three times more likely to have more intense breathlessness (OR 2.86; 95% CIs 1.46 to 5.62; p=0.002). No associations were seen with fentanyl nor with oxycodone.

**Conclusions:** This large, exploratory study identified 1 biologically plausible SNP that warrants further study in the response of breathlessness to morphine therapy.

**Strengths and limitations of this study**

- This is the first study that seeks to identify any candidate single nucleotide polymorphisms that help to predict differences in breathlessness intensity while on morphine.
- This is a population-based study using rigorous methodologies.
- The cohort used are taken from clinical practice across a range of clinical settings and countries.
- There is no replication cohort in this study—this is a topic for further work.
- This study has only sought signal from a bank of candidate genes.

**INTRODUCTION**

Breathlessness that persists despite disease-modifying treatment (refractory breathlessness) is a major clinical problem internationally.1,2 Chronic causes include respiratory disease (mainly chronic obstructive pulmonary disease (COPD) and interstitial lung disease), cardiac failure, progressive neurological disorders, cancers and cachexia in any late-stage disease.3–5 Symptom control is a key priority for people with a life-limiting illness as well as for their caregivers.6

Experimental studies of people with COPD and in healthy volunteers have shown that endogenous and exogenous opioids modulate the perception of breathlessness intensity without diminishing the ability to breathe during exercise or with resistive loads.7–9 In phase III clinical trials, the regular and systematic use of low doses of morphine (≤30 mg morphine/24 h) have been shown to safely reduce chronic refractory breathlessness intensity by a clinically meaningful extent.10–14

In the only formal dose-ranging study of opioids for the reduction of breathlessness intensity, the opioid dose needed to relieve breathlessness is highly individual, with a threefold difference of the dose required to relieve breathlessness, and where there was...
only a weak association between the severity of breathlessness and the dose of low-dose, sustained-release morphine providing relief. Clinico-demographic factors predicting response of breathlessness intensity to opioids from pooled data included higher baseline intensity of breathlessness and younger age. In this analysis, breathlessness intensity was not predicted by the dominant aetiology of breathlessness, gender, functional status nor descriptors of the breathlessness.

Clinically, large interindividual variations are also seen in the doses of opioids required to relieve pain in the palliative care population. The European Pharmacogenetic Opioid Study (EPOS), the largest such study in the world (n=2294), failed to find any single nucleotide polymorphisms (SNPs) from 112 candidate SNPs on 25 genes involved in opioid receptors, signalling, nor pain-modifying functions that explained any of the variations in the opioid dose required to achieve a symptomatic response to opioids for pain. This was in contrast with smaller studies which had identified several SNPs purportedly influencing the dose–response relation-ship. To date, no studies exploring genetic variability related to opioids and the palliation of refractory breathlessness have been conducted.

The aim of this hypothesis-generating, secondary analysis of the EPOS data is to identify possible candidate SNPs from a selection identified in the literature known to be associated with opioid pharmacology in order to inform future and prospective pharmacogenetic studies of the response of refractory breathlessness to opioids. This builds on the investigation of other key symptoms for people at the end of life including pain, nausea and cachexia from the same observational cohort.

This study tests the null hypothesis that genetic variations in selected candidate SNPs related to opioid receptors, signalling or pain-modifying functions are not associated with the intensity of breathlessness in people already treated with opioids for pain, assuming a similar distribution of pain and breathlessness scores across the population, and that opioid doses had been titrated to clinical effect. Importantly, this study is not exploring SNPs for breathlessness per se, or any relationship between SNPs and response to opioids in breathlessness intensity because of its cross-sectional design, but instead, SNPs which may influence a relationship between breathlessness intensity scores and opioids in people already on opioids for pain.

**METHODS**

Methods have been outlined in detail in previous papers from the group.

**Study setting**

This cross-sectional study included 17 centres from 11 European countries.

In the subgroup of people using morphine with collected breathlessness intensity scores (n=838), 112 candidate SNPs in 25 genes (table 1) with a putative influence on opioid receptors, signalling or pain modulation were evaluated for any association with breathlessness intensity scores, controlling for key factors that may influence breathlessness intensity or response to opioids. This analysis was repeated separately for people on fentanyl (n=405) or oxycodone (n=429).

**Study participants**

Inclusion criteria were: age 18 years or over; confirmed diagnosis of cancer; and regular use of a WHO step 3 opioid for moderate or severe pain related to the cancer or its treatment for more than 3 days. The only exclusion criterion was the inability to use the language spoken in the treating cancer centre.

**Data collection**

Between February 2004 and April 2008, cross-sectional phenotypic data were collected on the cohort including gender, age, weight, height, ethnicity, cancer diagnosis and sites of metastatic disease, the European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC-QLQ-C30; V3.0) and performance status (Karnofsky Performance Status scale). Data related to opioids included type of opioid, total opioid dose in the 24 h prior to blood sampling, duration of opioid therapy, and past use of other opioids. Breathlessness intensity was evaluated from question 8 in the EORTC QLQ-C30 on a four-point categorical verbal rating scale (not at all; a little; quite a bit; or very much) covering the person’s experience of the symptom over the previous week, reflecting the sensory-perceptual experience of the American Thoracic Society’s recent statement on the Mechanisms, Assessment and Management of Dyspnea.

**Specimen collection and analysis**

A single specimen of whole blood was collected in an EDTA tube at the time of questionnaire completion and stored at ~80°C before batched shipping to the HUNT Biobank in Levanger, Norway. DNA was extracted using Puregene blood kit (Qiagen Science, Germantown, Maryland, USA) and using technology from Applied Biosystems (Foster City, California, USA): the genotyping was done using the SNPlex (dry DNA Genotyping System; capillary electrophoresis; gene mapping (V4.0 software); and two SNPs (rs4680 and rs1045642) were extracted using TaqMan SNP allelic discrimination.

**Data analysis**

Separate analyses were conducted for each of three mutually exclusive populations (those who were prescribed only one opioid: morphine, oxycodone, or fentanyl), and for each of four modes of inheritance (dominant, recessive, codominant and overdominant). For each population, SNPs that were not in Hardy-Weinberg equilibrium, or had minor allele frequencies (<5%) were removed from the analysis, leaving...
significantly less than 0.05 (two-tailed) is considered statistically
violating the proportional odds assumption for any of the
guidelines.24

The REporting of Genetic Association Studies (STREGA)
participant provided written, informed consent. All analyses were
certified Research Ethics Committee at
approved the study, and each par-
to remove extraneous SNPs in high linkage disequi-
the model, it was neces-
ythnic frequency of each variant is also outlined (table 2).

The allele frequency was 72.3% (C) and 27.7% (T).

Other HTR3B SNPs tested included rs11214763,
ang for age, gender, BMI, Karnofsky status, time on opioids,
do any of the three opioids studied. For these analyses, a $p$ value less
(20%).22

The associations between breathlessness and any SNPs
identified as significant using the BH procedure, within
each mode of inheritance and each opioid prescribed,
were then examined using multivariable ordinal logistic
regression, clustering over country, and adjusting for
age, gender, BMI, Karnofsky status, time on opioids,
 opioid dose, pain levels and the SNPs identified by the
BH procedure. In order to fit the model, it was neces-
ary to remove extraneous SNPs in high linkage disequi-
librium, with $D^\prime>0.95$.23 The model reported did not
violate the proportional odds assumption for any of the
three opioids studied. For these analyses, a $p$ value less
than 0.05 (two-tailed) is considered statistically
significant.

All analyses were conducted using Stata V.13.1
(Statacorp, Texas, USA).

A properly constituted Research Ethics Committee at
each participating site approved the study, and each
participant provided written, informed consent.

The study is reported according to the STrengthening
the REporting of Genetic Association Studies (STREGA)
guidelines.24

112, 105 and 104 SNPs of interest in each of the mor-
phine, oxycodone and fentanyl populations, respectively.
Univariable associations between each SNP and the four-
point categorical rating scale for breathlessness were
determined using Fisher’s exact test. To control the
overall family-wise type I error rate (FWE) within each
mode of inheritance and for each opioid, we used
Benjamini-Hochberg (BH) multiple hypothesis testing
with a false discovery rate (FDR) set at 20%.22

The clinico-demographic factors for the 1672 partici-
pants in this substudy are outlined in table 1 for the
cohorts taking each of the three opioids.

Eight hundred and thirty-eight people were taking
morphine in whom viable samples were available for 588.
For these people, four variants on the β2 arrestin gene
(ARRB2) and one on the 5-hydroxytryptamine type 3B
(HTR3B rs7103572) gene were associated in univariable
analyses with breathlessness intensity (table 2). The geno-
typic frequency of each variant is also outlined (table 2).
Additionally, morphine dose and worsening functional
(Karnofsky) status were significantly associated with more
intense breathlessness in univariable analyses (table 3).
In the multivariable model, three of the ARRB2 variants
were excluded as all variants were in high linkage disequi-
librium with Lewontin’s25 normalised linkage disequi-
librium parameter $D^\prime>0.95$ for each pair of SNPs (where a
value of $D=0$ indicates independence and $D=1$ complete
dependence of SNP frequencies).

Significance was only maintained for the HTR3B
(rs7103572) and functional status (table 3). There was
no interaction between HTR3B (rs7103572) and opioid
dose. There were no significant findings in the oxyc-
odone or fentanyl cohorts.

The HTR3B (rs7103572) genotype frequency (TT)
was 8.2% of participants, with 52.8% CC and 39.1% CT.
The allele frequency was 72.3% (C) and 27.7% (T).
Other HTR3B SNPs tested included rs11214763,
rs11606194, rs1176744, rs2276307, rs3782025, rs1672717
and rs7943062.

Table 1 112 Predefined candidate single nucleotide polymorphisms (SNPs) in 25 genes with a putative influence on opioid
receptors, signalling and pain modulation: OPRM1, OPRD1, OPRK1, ARRB2, GNAZ, HINT1, Stat6, ABCB1, COMT, HTR1A,
ADRA2A, MC1R, TACR1, GCH1, DRD2, DRD3, HTR3A, HTR3B, HTR2A, HTR3C, HTR3D, HTR3E, HTR1A, UGT2B7 or CNR1

<table>
<thead>
<tr>
<th></th>
<th>Morphine (n=838)</th>
<th>Fentanyl (n=405)</th>
<th>Oxycodone (n=429)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62.1 (12.1)</td>
<td>63.5 (12.6)</td>
<td>62.3 (12.3)</td>
</tr>
<tr>
<td>Female gender</td>
<td>394 (47.0)</td>
<td>202 (49.9)</td>
<td>188 (43.8)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.1 (4.7)</td>
<td>23.2 (4.6)</td>
<td>23.9 (4.3)</td>
</tr>
<tr>
<td>Karnofsky*</td>
<td>60 (50–70)</td>
<td>60 (40–70)</td>
<td>70 (50–80)</td>
</tr>
<tr>
<td>Time on opioids (months)*</td>
<td>1 (0–4)</td>
<td>1 (0–4)</td>
<td>1 (0–4.5)</td>
</tr>
<tr>
<td>24 hourly opioid dose*</td>
<td>60 mg (40–120 mg)</td>
<td>50 µg (25–75 µg)</td>
<td>60 mg (40–120 mg)</td>
</tr>
</tbody>
</table>

The population characteristics of the three cohorts of patients on opioids in the European Palliative Outcomes Study (mean (SD), median
(IQR*) or n (%)).

*IQR=(Lower quartile
− upper quartile).

Table 2 The significant single nucleotide polymorphisms for the recessive mode of inheritance for morphine users (Fisher’s exact test) and the frequency of these minor alleles

<table>
<thead>
<tr>
<th>Morphine</th>
<th>p Value</th>
<th>Variant</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARRB2_rs3786047</td>
<td>0.0010</td>
<td>AA vs (AG+GG)</td>
<td>77 (9.6)</td>
</tr>
<tr>
<td>ARRB2_rs2036657</td>
<td>0.0045</td>
<td>GG vs (AG+AA)</td>
<td>79 (9.9)</td>
</tr>
<tr>
<td>ARRB2_rs2271167</td>
<td>0.0052</td>
<td>AA vs (AG+GG)</td>
<td>77 (9.9)</td>
</tr>
<tr>
<td>ARRB2_rs1045280</td>
<td>0.0069</td>
<td>CC vs (CT+TT)</td>
<td>81 (10.1)</td>
</tr>
<tr>
<td>HTR3B_rs7103572</td>
<td>0.0070</td>
<td>TT vs (CC+TC)</td>
<td>48 (8.2)</td>
</tr>
</tbody>
</table>
DISCUSSION

In this study, people taking morphine for cancer pain and with both rs7103572 allele variants of the 5HT3B gene were three times more likely to have more intense breathlessness having controlled for other available factors. This finding was not mirrored in those taking oxycodone or fentanyl.

Breathlessness, like pain, is a phenotype with complex biological interactions. Studies have shown only weak associations between the underlying aetiology of breathlessness, the descriptors of sensation and a tailored treatment for breathlessness. The degree of physiological impairment (such as hypoxaemia or forced expiratory volume in 1 s) and a person’s subjective sensation of breathlessness are weakly correlated and do not explain much of the interindividual and intrindividual variations observed with the subjective sensation of breathlessness. Therefore, other factors need to be identified that help to understand the variations in the benefits and toxicities of people’s clinical responses. Identifying potential factors associated with response, such as the HTR3B, has the potential to help reconcile clinical experience with objective factors that explain population differences. It is likely that several factors contribute to the reported threefold variation in breathlessness response to morphine observed in the dose titration study. Other, as yet unknown factors, must be contributing to this variation in response to opioids, so any factor that helps to unravel variations in response of breathlessness to opioids is likely to be of value to clinicians and researchers given the paucity of such factors currently. These current findings of one potential SNP would form the basis of a prospective study in which opioids were introduced to people with refractory breathlessness to opioids is likely to be of value to clinicians and researchers given the paucity of such factors currently. These current findings of one potential SNP would form the basis of a prospective study in which opioids were introduced to people with refractory breathlessness to opioids is likely to be of value to clinicians and researchers given the paucity of such factors currently. 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Borg scales, may be preferable in this population, Likert scales for reviews of large numbers of symptoms are a reasonable approach. It is also worth noting that these screening tools make no distinction between the affective component of breathlessness (unpleasantness) and its intensity (severity). Any prospective study would need to separate these two components of breathlessness and reflect the person’s emotional response.

Strengths of the study
Many genetic association studies have not been reproducible. By contrast, the current study has several key strengths that increase confidence in the finding that a particular SNP might influence morphine-induced modulation of the sensation of breathlessness:

- A plausible biological mechanism;
- Large number of patients (including enough to include relevant clinical and demographic covariates in the analytic models);
- A study population broadly representative of people with advanced cancer;
- A large number of genes and candidate SNPs;
- Rigorous statistical methods to deal with the problem of multiplicity;
- Seeking a signal that is sufficient to be clinically meaningful;
- Use of well-validated assessment tools in rigorously translated versions for the participating countries.

Limitations
The study did not specify a particular mode of inheritance as primary, and therefore, our results do not control the FWE within the population. The study addressed this by creating sensitivity analyses that aggregated all comparisons for different modes of inheritance with each population and applied the BH procedure for multiple comparisons. As such, the study did not find any other significant SNPs until the FDR was set at 50% or greater.

This study only explored individual candidate SNPs and did not explore gene–gene interactions. A negative result does not rule out important SNPs on other parts of candidate genes or on other genes. The study does not contribute to candidate SNPs for the perception of breathlessness itself, only the degree of perception of breathlessness while on opioids for pain.

The change in symptom severity in this cross-sectional study population is unknown, and we are therefore unable to draw conclusions about breathlessness response to opioids. Only longitudinal studies before and after the introduction of opioids for breathlessness can fully answer this question. Some respondents with breathlessness may have partially responded to opioids for the intensity of their breathlessness, and be much worse without them, others may not have responded to opioids at all, and yet others with no breathlessness may have had none prior to starting opioids.

Implications for further research
There is a need to replicate these findings in a similar independent cohort. There would be an argument for using one of the newer, more comprehensive measures of breathlessness that includes measures of severity, unpleasantness and the person’s emotional response. Using such measurement tools would allow for a more nuanced exploration of the response to opioids for breathlessness.

Genome-wide association studies may identify genetic variations that are important in the explanation of varying responses of breathlessness to opioids as these studies become more affordable.

CONCLUSIONS
This large, exploratory study identified one SNP associated with higher levels of breathlessness in people taking morphine for pain, but not in those taking fentanyl or oxycodone. The study does not help to understand any genetic variations associated with the perception of breathlessness per se, but provides a candidate SNP for further exploration in prospective studies of people before and after morphine is introduced to reduce the perception of breathlessness.

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Acknowledgements The authors thank all the participating sites; the investigators in the main study; the Norwegian University of Science and Technology (NTNU); and all the people who gave their time and energy to create this unprecedented data set. They also thank Dr Ying-Xian Pan for his insightful comments on the manuscript.

Contributors DC and MJ did the literature search. DC, PK and AS provided the study design. SK and PK collected the data. SQ, AS, PK, MJ and DC performed the data analysis. All authors assisted in the data interpretation, writing and final approval of the manuscript.

Funding Funding for the specimen collection and the genetic evaluation was granted through the European Palliative Care Research Collaborative, the Norwegian Research Council, the Norwegian University of Science and Technology and the European Union’s Sixth Framework (contract number 037777).

Competing interests None declared.

Ethics approval Research Ethics Committee of each participating site.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement These data are made available to researchers on request to the European Palliative Care Research Network which is...
responsible for the European Pharmacogenetic Opioid Study coordinated through Trondheim University, Norway. pal.klepstad@ntnu.no Data on all 2294 participants is available in an annotated database.

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*BMJ Open* 2015 5:

doi: 10.1136/bmjopen-2014-006818

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