Use of clinical phenotypes to characterize emergency department patients administered intravenous opioids for acute pain

Mordechai Caplan¹, Benjamin W. Friedman², Jason Siebert², Mai Takematsu², Victoria Adewunmi², Chiraag Gupta², Deborah J. White², Eddie Irizarry²

¹Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY, USA
²Department of Emergency Medicine, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY, USA

Objective Individual experience with opioids is highly variable. Some patients with acute pain do not experience pain relief with opioids, and many report no euphoria or dysphoric reactions. In this study, we describe the clinical phenotypes of patients who receive intravenous opioids.

Methods This was an emergency department-based study in which we enrolled patients who received an intravenous opioid. We collected 0 to 10 pain scores prior to opioid administration and 15 minutes after. We also used 0 to 10 instruments to determine how high and how much euphoria the patient felt after receipt of the opioid. Using a cutoff point of ≥50% improvement in pain and the median score on the high and euphoria scales, we assigned each participant to one of the following clinical phenotypes: pain relief with feeling high or euphoria, pain relief without feeling high or euphoria, inadequate relief with feeling high or euphoria, and inadequate relief without feeling high or euphoria.

Results A total of 713 patients were enrolled, 409 (57%) of whom reported not feeling high, and 465 (65%) reported no feeling of euphoria. Median percent improvement in pain was 37.5% (interquartile range, 12.5%–60.0%). One hundred seventy-eight participants (25%) were classified as experiencing pain relief with euphoria or feeling high, 190 (27%) experienced inadequate relief with euphoria or feeling high, 101 (14%) experienced pain relief without euphoria or feeling high, and 244 (34%) reported inadequate relief without euphoria or feeling high.

Conclusion Among patients who receive intravenous opioids in the emergency department, the experiences of pain relief and euphoria are highly variable. For many, pain relief is independent of feeling high.

Keywords Opioid analgesics; Morphine; Hydromorphone; Euphoria; High
INTRODUCTION

Individual experience with opioids is highly variable. Some patients do not experience pain relief when administered therapeutic doses of intravenous (IV) opioids [1–3]. Similarly, emergency department (ED) patients with acute pain exposed to opioids report variable euphoric experiences, with many reporting no euphoria or dysphoric reactions [4–6]. For emergency physicians, use of parenteral opioids has become fraught. Increasing awareness of the long-term sequelae of opioid exposure impacts the risk-benefit calculation even though most opioid-naive patients exposed to opioids in the ED will not transition to opioid use disorder [7–10]. It is important to understand which patients exposed to opioids in the ED are at risk of this transition. Unfortunately, instruments such as the Opioid Risk Tool, which have some utility in the outpatient setting, have proved ineffectual among ED patients [8,11].

More work is needed to understand which ED patients exposed to opioids are at risk of poor long-term outcomes. To further this goal, we delineated four clinical phenotypes: (1) pain relief with feeling high or euphoria; (2) pain relief without feeling high or euphoria; (3) inadequate relief with feeling high or euphoria; and (4) inadequate relief without feeling high or euphoria. Presumably, patients who are administered IV opioids and experience pain relief with euphoria or feeling high are at highest risk of transition to opioid use disorder. Those who experience pain relief without euphoria or feeling high may be the most suitable for opioid use.

In this study, we assigned clinical phenotypes to ED patients with pain who received IV opioids using standardized scales to measure pain relief and euphoria shortly after exposure to the opioids. These clinical phenotypes can potentially be used in subsequent studies to predict risk of transition to opioid use disorder.

METHODS

Ethics statement
The study was approved by the Institutional Review Board of Albert Einstein College of Medicine (No. 2019-10482). All participants provided written informed consent for publication of the research details.

Study design and setting
Data were obtained from an observational study designed to determine the risk of persistent opioid use among ED patients with severe pain who received IV opioids. The goal of our analysis was to define clinical phenotypes based on two axes: pain relief and feeling high or euphoria. These data were collected between February 2021 and June 2022.

The study was conducted in the two academic EDs of Montefiore Medical Center (Bronx, NY, USA). Research associates staffed the EDs throughout the study period and gathered all outcome data.

Selection of participants
We included any adult patient (≥18 years) who presented to the ED with pain of sufficient severity that the initial treatment was an IV opioid. We excluded patients who did not have the capacity to understand the consent process in English or Spanish or if they refused to participate. Neither type nor dose of IV opioid was standardized for this protocol—this was left to the clinical team and based on perceived need, typical practice, and clinician experience.

Measurements
All data were obtained through interview with the study participant, with the exception of type and dose of opioid administered and discharge diagnosis, which were obtained by chart review (study participants would not necessarily have access to these.
We asked all participants whether they had used any pain medication (and if yes, which one) in the previous 6 months.

To measure feeling high and euphoria, we relied on instruments originally developed as part of the Addiction Research Center Inventory, a comprehensive questionnaire used to determine the subjective effects of psychoactive substances [12]. The items we used have been validated for use among recreational opioid users [13,14] and refined among ED patients with acute pain [4–6]. For this study, we used a two-item instrument: (1) What was your level of feeling high with the medication? (2) What was your level of euphoria, joy, or happiness with the medication? Responses were recorded on an 11-point integer scale with 0 defined as “none” and 10 as “the highest level imaginable.” We anticipated a fair amount of overlap between feeling high and euphoria, joy, or happiness but we thought some respondents might experience feeling high as a dysphoric experience and some might experience euphoria but would not want to stigmatize the feeling by labeling it as feeling high; thus, we included both items in our interview. Euphoria and feeling high were assessed 15 minutes after the IV opioid was administered so that participants could describe the sensation as it was occurring. Participants were also asked to respond to the following open-ended prompt: “Please describe the effects of the opioid medication.”

Pain intensity was assessed on a validated 11-point integer scale (0, no pain; 10, the worst pain imaginable) commonly used in ED research [15,16]. Pain intensity was assessed before the IV opioid was administered and again 15 minutes later.

Outcomes
The primary outcome was assignation of each participant to one of four clinical phenotypes: (1) pain relief with feeling high or euphoria; (2) pain relief without feeling high or euphoria; (3) inadequate relief with feeling high or euphoria; and (4) inadequate relief without feeling high or euphoria. We report the frequency of each of these clinical phenotypes within our cohort.

Statistical analysis
We report graphically the distribution of scores for “What was your level of feeling high with the medication?” and “What was your level of euphoria, joy, or happiness with the medication?” Because there is no defined cutoff point for these scales (feeling high vs. not and euphoria vs. none), we determined the impact of euphoria or feeling high based on the median response (this turned out to be 0 vs. ≥1) versus 5, the middle of the 0 to 10 scale. We also report the concordance between the feeling high and euphoria scores using a cross-tabulation table. Our a priori definition of feeling high or euphoria was a score at or above the median for either of the two items.

We also report the distribution of pain relief scores (baseline pain – 15-minute pain) and the percent improvement calculated using the following formula: (baseline pain – 15-minute pain)/baseline pain. We considered adequate pain relief to be an improvement in pain ≥50%. We examined the association between pain relief and feeling high or euphoria using Spearman rho.

We also report feeling high and euphoria scores for all patients who reported use of pain medication in the previous 6 months by type of pain medication.

RESULTS

Characteristics of study subjects
During the 17-month enrollment period, 713 patients were enrolled and provided complete data. Baseline characteristics of the cohort are depicted in Table 1. Of the cohort, 679 (95%) received morphine and 34 (5%) received hydromorphone. The median morphine dose was 4 mg (interquartile range [IQR], 4–4 mg), the median hydromorphone dose was 2 mg (IQR, 1–2 mg).

Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value (n = 713)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>48 ± 16</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>455 (64)</td>
</tr>
<tr>
<td>Male</td>
<td>257 (36)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Diagnostic grouping</td>
<td></td>
</tr>
<tr>
<td>Nonspecific abdominal pain</td>
<td>267 (37)</td>
</tr>
<tr>
<td>Kidney stone</td>
<td>189 (27)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>81 (11)</td>
</tr>
<tr>
<td>Musculoskeletal (not including back pain)</td>
<td>47 (7)</td>
</tr>
<tr>
<td>Gynecological</td>
<td>34 (5)</td>
</tr>
<tr>
<td>Biliary</td>
<td>30 (4)</td>
</tr>
<tr>
<td>Back pain</td>
<td>24 (3)</td>
</tr>
<tr>
<td>Other</td>
<td>41 (6)</td>
</tr>
<tr>
<td>Initial pain score</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>411 (58)</td>
</tr>
<tr>
<td>8 or 9</td>
<td>222 (31)</td>
</tr>
<tr>
<td>≤7</td>
<td>80 (11)</td>
</tr>
<tr>
<td>Admitted to the inpatient service</td>
<td>303 (42)</td>
</tr>
<tr>
<td>Opioid exposure within the previous 6 months†</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>131 (18)</td>
</tr>
<tr>
<td>No</td>
<td>582 (82)</td>
</tr>
</tbody>
</table>

Values are presented as number (%) or mean ± standard deviation.
†Use of oral or parenteral opioids.
median (IQR) score for feeling high was 0 (0–5), and that for euphoria was 0 (0–4). Using score ≥ median on either scale, 368 patients (52%) were categorized as having experienced feeling high or euphoria. When we used the more stringent criteria of score > 5 on either of the 0 to 10 scales, 273 participants (38%) were categorized as having experienced euphoria or feeling high. Agreement between the “feeling high” and “euphoria, joy, or happy” scales is depicted in Table 2.

Median improvement in 0 to 10 pain score between baseline and 15 minutes was 3 (IQR, 1–6). Median pain improvement was 37.5% (IQR, 12.5%–60.0%) (Fig. 1C). Improvement in pain score was associated with feeling high (rho, 0.22; P < 0.01) and euphoria (rho, 0.23; P < 0.01). Median (IQR) pain and euphoria or feeling high scores for each phenotype are reported in Table 3. Impact of the type of opioid received and diagnosis on clinical phenotype is presented in the Supplementary Tables 1 and 2.

The following were the most common descriptors used by patients to describe the effects of opioids: lightheaded or dizziness (n = 147); drowsy, tired, or sleepy (n = 114); good or better (n = 87); relaxed or mellow (n = 38); warm or hot (n = 32); and drugged, drunk, or woozy (n = 8).

Among 260 patients who reported use of any pain medication in the previous 6 months, median (IQR) feeling high and euphoria scores were 0 (0–6) and 0 (0–5), respectively. For 53 patients who reported use of oxycodone within the previous 6 months, median (IQR) for feeling high and euphoria were 0 (0–3) and 0 (0–3), respectively. For 15 patients who reported use of morphine within the previous 6 months, these respective scores were 0 (0–10) and

### Table 2. Cross-tabulation of feeling high versus euphoria, joy, or happiness

<table>
<thead>
<tr>
<th>Feeling high</th>
<th>Euphoria, joy, or happiness</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1–3</td>
</tr>
<tr>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>1–3</td>
<td>24</td>
</tr>
<tr>
<td>4–7</td>
<td>22</td>
</tr>
<tr>
<td>8–10</td>
<td>18</td>
</tr>
</tbody>
</table>

Values are presented as number of participants in each category.

### Table 3. Clinical phenotypes of patients who received opioids in the emergency department

<table>
<thead>
<tr>
<th>Clinical phenotype</th>
<th>Pain improvement (%)</th>
<th>Score (range, 0–10)</th>
<th>Any exposure to opioids during the preceding 6 months[a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain relief with feeling high or euphoria (n = 178, 25%)</td>
<td>70 (60–100)</td>
<td>Feeling high</td>
<td>Euphoria, joy, or happiness</td>
</tr>
<tr>
<td>No pain relief with feeling high or euphoria (n = 190, 27%)</td>
<td>22 (11–33)</td>
<td>5 (2–8)</td>
<td>2 (0–5)</td>
</tr>
<tr>
<td>Pain relief without feeling high or euphoria (n = 101, 14%)</td>
<td>67 (50–90)</td>
<td>0 (0–0)</td>
<td>0 (0–0)</td>
</tr>
<tr>
<td>No pain relief without feeling high or euphoria (n = 244, 34%)</td>
<td>14 (0–30)</td>
<td>0 (0–0)</td>
<td>0 (0–0)</td>
</tr>
</tbody>
</table>

Values are presented as median (interquartile range) or number (%).

[a] Use of oral or parenteral opioids.
0 (0–7). These scores for 11 patients who reported use of hydro- 
morphone within the previous 6 months were 4 (0–7) and 0 (0– 
5), respectively.

**DISCUSSION**

In this analysis of 713 ED patients who received IV opioids for 
pain, we found highly variable responses to both pain relief and 
euphoria or feeling high, with about half of the sample reporting 
some indication of euphoria or feeling high and about one-third 
reporting ≥ 50% pain relief. About two-thirds of the sample re-
ported little to no sensations of being high, and a comparable 
percentage reported no or minimal feelings of euphoria. Only 
14% of the sample reported the ideal outcome of pain relief 
without feeling high or euphoria. Absence of an opioid effect was 
the most common clinical experience: one-third of the sample 
reported inadequate pain relief and no feelings of high or eupho-
ria. Other interesting findings include discordance between the 
reports of levels of feeling high and euphoria, joy, or happiness 
caused by the medication and the disconnect for many patients 
between pain relief and euphoria or feeling high.

As evidenced by cross-tabulation, feeling high or feeling joy, 
happiness, and euphoria are not necessarily the same experience. 
More than 10% of the sample reported feeling euphoric without 
feeling high or vice versa, as evidenced by patients who described 
feeling “drunk,” “groggy,” or “drugged.” Patients who reported 
feeling euphoric without feeling high may have been reluctant to 
associate the positive experience with a word that has negative 
societal connotations.

Our analysis highlights the need for a more patient-centered 
understanding of opioid-induced euphoria. A one-size-fits-all ap-
proach to opioid practice is likely inappropriate for a large num-
ber of patients. Many patients may benefit from opioids without 
substantial risk, while others may be exposed to risk without ex-
periencing notable benefit.

Limitations of this study should be mentioned. First, the scales 
used to assess pleasurable sensations were initially developed and 
validated in a nonclinical arena among healthy volunteers and 
recreational substance users. While these have been used among 
patients with acute pain in the ED, they scales have not been for-
mally validated in such a setting. Also, these scales are subjective 
and require open participation. We cannot know if some partici-
pants did not answer truthfully due to the perceived stigma asso-
ciated with feeling high. Furthermore, the order of questions may 
have influenced participant response to the questions: we asked 
first about feeling high and then about euphoria, joy, or happi-
ness; finally, we elicited responses with an open-ended question.

By asking about feeling high first, we may have biased subse-
quent responses.

Furthermore, to assign participants to different phenotypes, we 
had to choose cutoff points at which to dichotomize the 0 to 10 
scales. For the scales for feeling high or euphoria, existing data 
do not help identify a cutoff point. Fortunately, the median on 
these scales corresponded to the intuitive cutoff point of 0/1. 
Thus, patients either experienced some euphoria or feeling of 
high or none at all. However, this may have resulted in miscate-
gorization of some patients who reported scores of 1 or 2 but re-
ally had no meaningful euphoric feelings.

Finally, we did not control or measure how the opioid was ad-
ministered. A rapid IV push may be associated with a more eu-
phoric experience than a slower IV infusion.

In conclusion, among patients who received IV opioids in the 
ED, the experience with pain relief and euphoria or feeling high 
was highly variable. For many patients, pain relief was indepen-
dent of feeling high or euphoria.

**SUPPLEMENTARY MATERIALS**

Supplementary Table 1. Clinical phenotype based on opioid re-
ceived

Supplementary Table 2. Clinical phenotype based on common 
discharge diagnoses

Supplementary materials are available from https://doi.org/10. 
15441/ceem.23.018.

**ETHICS STATEMENT**

The study was approved by the Institutional Review Board of Al-
bert Einstein College of Medicine (No. 2019-10482). All partici-
pants provided written informed consent for publication of the 
research details.

**CONFLICT OF INTEREST**

No potential conflict of interest relevant to this article was re-
ported.

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AUTHOR CONTRIBUTIONS
Conceptualization: BWF, EI; Methodology: BWF, EI; Data curation: BWF, MT, VA, CG, DJW, EI; Formal analysis: MC, BWF, JS; Validation: BWF, JS; Writing–original draft: MC, BWF; Writing–review & editing: all authors. All authors read and approved the final manuscript.

ORCID
Mordechai Caplan  https://orcid.org/0000-0002-9164-5546
Benjamin W. Friedman  https://orcid.org/0000-0002-2753-5860
Jason Siebert  https://orcid.org/0000-0003-3777-7916
Mai Takematsu  https://orcid.org/0000-0002-5696-295X
Victoria Adewunmi https://orcid.org/0000-0002-6743-0588
Chiraag Gupta  https://orcid.org/0000-0002-1877-8916
Deborah J. White  https://orcid.org/0000-0001-5887-5465
Eddie Irizarry  https://orcid.org/0000-0001-5887-5465

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