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Association Between Commonly Prescribed Opioids and Androgen Deficiency in Men: A Retrospective Cohort Analysis

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Abstract

Objective. Androgen deficiency is common among men who use opioids daily for chronic pain. In previous studies, we found that long-acting opioids are associated with greater odds of androgen suppression than equipotent doses of short-acting opioids. Here we examined whether specific commonly prescribed opioids were associated with greater odds of androgen deficiency compared to hydrocodone.

Design. Retrospective cohort study.

Setting and Patients. Within a large, integrated health care delivery system, this study was comprised of men ages 18–80 on a stable regimen of a single opioid for chronic non-cancer pain.

Methods. Morning serum total testosterone levels were measured in subjects prescribed one opioid for at least 90 days. The association between individual opioids and androgen deficiency was assessed with logistic regression, controlling for dose, obesity, age, hypertension, hyperlipidemia, and diabetes, using hydrocodone as a referent.

Results. This study included 1,159 men. Men on fentanyl (odds ratio [OR] 25.7, 95% CI 2.82–234.97), methadone (OR 7.33, 95% CI 3.29–16.33), or oxycodone (OR 3.15, 95% CI 1.87–5.33) were more likely to be androgen deficient than men on hydrocodone. Increases in dose affected the odds of androgen deficiency differently for different opioids. Increased doses of hydrocodone (OR 1.18 per 10-mg increase in drug, 95% CI 1.09–1.28) and oxycodone (OR 1.01, 95% CI 1.00–1.02) were associated with increased odds of androgen deficiency.

Conclusions. Our results suggest that certain opioids are associated with increased odds of androgen deficiency compared with hydrocodone. Transdermal fentanyl, methadone and oxycodone were associated with higher odds of androgen deficiency than hydrocodone.

Key Words. Opioid; Chronic Pain; Long-Acting Opioid; Short-Acting Opioid; Hypogonadism; Testosterone

Introduction

Opioids are among the medications most frequently prescribed for pain worldwide, yet little is known about the medical risks associated with daily use of these drugs. The trend over the last 20 years has been to shift patients requiring daily opioid therapy to the use of long-acting opioids, with short-acting opioids for breakthrough pain as needed, although there are no data showing improved efficacy with this strategy [1–4]; neither do data exist showing risk differences between opioids, with the exception of the link between methadone and increased cardiac risk secondary to QT prolongation.

Androgen deficiency is a common, well-known risk with chronic, daily opioid use and can have serious and

expensive health consequences, including loss of libido, erectile dysfunction, depression, osteoporosis, muscle loss, and fatigue [5–7]. All of these can result in a reduction in quality of life for the patient and increased utilization of resources to treat these sequelae.

In two previous studies, we have shown that chronic use of long-acting opioids is associated with greater odds of androgen deficiency compared to chronic use of short-acting opioids [8,9]. We hypothesized that in men using opioids daily, constant drug levels may suppress the hypothalamic-pituitary-gonadal axis and that periodic lows or nadirs in their serum drug level are necessary in order to produce gonadotropin-releasing hormone, luteinizing hormone, and testosterone. Patients taking intermittent doses of short-acting opioids were more likely to experience these serum nadirs than patients on equipotent doses of long-acting opioids, which maintain a steady serum drug level.

If, as a class, long-acting opioids are more strongly associated with androgen deficiency, are specific long-acting opioids driving this? Similarly, are there short-acting opioids that are also suppressive, but whose effects are obscured when these drugs are analyzed as a class? To address this, we examined a subset of our study population of 1,585 men [8] who were on exactly one opioid to determine whether there is an association between any individual opioid and androgen deficiency. Providers have myriad options when it comes to opioid prescribing. Because there is no known difference in efficacy among opioids for chronic pain, differences in risk, if they exist, could better inform prescribing decisions.

Methods

This study was conducted at Kaiser Permanente Northern California (KPNC), a large integrated health care delivery system having approximately 3.2 million members. Administrative databases contain records of inpatient and outpatient utilization, pharmacy utilization, and lab test orders and results. The Kaiser Foundation Research Institute's Institutional Review Board approved this study with waiver of consent and waiver of authorization. Funding for this study was provided by the KPNC Community Benefit program.

Database Creation

Administrative records were utilized to identify men using opioids daily for non-cancer pain in the 100 days before a testosterone test. Cohort identification methods have been described previously [8]. Briefly, men ages 18 to 80 years who had a morning total testosterone test in the period from January 1, 2007, through December 31, 2011, were eligible for our study if they had purchased a minimum of 90 days' supply of one prescribed opioid, which we defined as one opioid substance regardless of formulation, in the outpatient setting within the 100 days before the testosterone test date (Table 1). In the case of oxycodone they may have

been using more than one formulation (i.e., extended-release plus immediate-release for breakthrough pain). All men using morphine in this cohort were exclusively using an extended-release formulation. Men with cancer, a history of cancer, or endocrine disorders other than stable treated hypothyroidism within the year before the test date were excluded.

Independent Variables

The primary risk factor of interest was the specific opioid the subject had purchased in the outpatient pharmacy setting in the 100 days before the testosterone test (see Table 1 for the opioids included).

The secondary risk factor was dose. We calculated dose in morphine standardized equivalents (MSE)[10]; our method of calculating dose for this cohort has been described previously [8].

Other covariates analyzed include age, obesity defined as $BMI \geq 30$ [11], diabetes [12], hypertension, hyperlipidemia, hypertension and statin use. These covariates have been associated with androgen deficiency in men [13–16], although the relationship may be bidirectional [17,18].

We assessed correlation between independent variables in preliminary analyses. Age, diabetes, hypertension, and hyperlipidemia were highly correlated with each other. This finding agrees with general clinical knowledge about age and these comorbidities. We therefore created a categorical variable containing counts of the comorbidities diabetes, hypertension, and hyperlipidemia, stratified by $age < 50$ years or ≥ 50 years. The reference for this variable was $age < 50$ years plus the absence of all three comorbidities. Obesity was not found to be highly correlated with age, diabetes, hypertension, or hyperlipidemia and therefore was analyzed as a separate covariate.

Table 1 Study population by opioid used

Drug	Duration of action	N	(%)
Codeine	Short	31	**(2.67)**
Fentanyl	Long	13	**(1.12)**
Hydrocodone	Short	859	**(74.12)**
Hydromorphone	Short	7	**(0.60)**
Methadone	Long	74	**(6.39)**
Morphine	Long	48	**(4.14)**
Oxycodone			
Oxycodone (SR)	Long	22	**(1.90)**
Oxycodone (SR) + Oxycodone (IR)	Mixed	33	**(2.85)**
Oxycodone (IR)	Short	72	**(6.21)**
Total	—	1159	**(100)**

Outcome

Androgen deficiency was defined as morning serum total testosterone < 250 ng/dL. KPNC and the Endocrine Society recommend using total testosterone rather than free testosterone for initial screening [19]. We used 250 ng/dL as the lower limit of normal based on our institution's assay. All laboratory studies were performed at the KPNC Regional Laboratory in Richmond, California. Total testosterone was determined using the Siemens Immulite 2000 testosterone assay (coefficient of variance 9.6% at 149 ng/dL and 11.1% at 521 ng/dL).

Statistical Methods

Univariate statistics are presented as counts, percentages, medians, and interquartile ranges. Bivariate analyses of binomial variables were performed using chi-square tests; where androgen deficiency percentages were compared across individual drugs, chi-square tests were performed with bootstrap resampling to correct for multiple comparisons. Comparisons of androgen deficiency across age and dose were made using the Wilcoxon-Mann-Whitney nonparametric test. Multivariable analyses were performed using logistic regression. Where an independent variable was suspected of modifying the association between another independent variable and androgen deficiency, as in the case of dose and opioid, an interaction term was created by taking the product of the two variables. This interaction term was entered into the logistic regression model; where it was found to be significant, we determined that interaction was present. Results were considered significant at $P < 0.05$ or, in the case of odds ratios (ORs), where 95% CIs did not cross 1.00. Analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC).

Results

Of the initial cohort of 1,585 men [8], 1,159 were using exactly one of the opioids listed in Table 1 in the 100 days before undergoing a total testosterone test. Most subjects on long-acting opioids were also using a different short-acting opioid for breakthrough pain; therefore only 190 of 616 subjects on long-acting opioids (30.8%) were included. All 969 subjects in the short-acting group from the larger cohort were using one opioid only and were therefore included. Population demographics by individual opioid are presented in Table 2.

Bivariate Analysis

Of subjects on fentanyl, 69.2% were androgen deficient, as were 60.8% of those on methadone, 52.1% of those on morphine, 50.4% of those on oxycodone, 42.9% of those on hydromorphone, 35.5% of those on codeine, and 34.2% of those on hydrocodone. In assessing the association between opioid and androgen deficiency across all pairs of opioids, two comparisons were

Table 2 Population demographics by opioid

Demographic variable	Codeine N = 31	Fentanyl N = 13	Hydrocodone N = 859	Hydromorphone N = 7	Methadone N = 74	Morphine N = 48	Oxycodone N = 127
Age, median (IQR)	58 (53–65)	56 (52–63)	53 (46–61)	52 (51–72)	51 (44–58)	57.5 (52.5–63)	52 (43–60)
Dose, median (IQR)	0.6 (0.45–0.9)	150 (100–300)	30 (20–40)	64 (48–96)	150 (75–300)	90 (52.5–157.5)	60 (30–240)**
Testosterone, ng/dL median(IQR)	288 (232–374)	203 (108–371)	308 (218–415)	369 (138–381)	206 (115–328)	215.5 (163–354.5)	240 (164–374)
Obese*, N (%)	11 (40.7%)	5 (41.7%)	398 (47.6%)	2 (28.6%)	32 (43.8%)	19 (40.4%)	56 (45.5%)
Diabetes, N (%)	4 (12.9%)	1 (7.7%)	157 (18.3%)	2 (28.6%)	11 (14.8%)	7 (14.6%)	14 (11.0%)
Hypertension, N (%)	18 (58.1%)	6 (46.2%)	511 (59.5%)	4 (57.1%)	46 (62.2%)	25 (52.1%)	75 (59.1%)
Hyperlipidemia, N (%)	11 (35.5%)	6 (46.2%)	350 (40.8%)	3 (42.9%)	21 (28.4%)	10 (20.8%)	50 (39.4%)
Statin use, N (%)	12 (38.7%)	2 (15.4%)	312 (36.3%)	2 (28.6%)	22 (29.7%)	17 (35.4%)	41 (32.3%)

IQR = interquartile range.
*BMI data were missing for 34 subjects.
**Subjects taking long-acting oxycodone, with or without short-acting oxycodone, have a median dose of 270 mg MSE (IQR 120–570), whereas those taking short-acting oxycodone have a median dose of 43.5 mg MSE (IQR 30–60).

Table 3 Unadjusted rates of androgen deficiency by clinical characteristic

Clinical characteristic	Not androgen deficient	Androgen deficient (total testosterone $\leq$ 250 ng/dL)	P Values*
Obese**			
Obese	266 (50.9%)	257 (49.1%)	<0.001
Not obese	420 (69.8%)	182 (30.2%)	
Diabetes			
Diabetes	98 (50.0%)	98 (50.0%)	<0.001
No diabetes	610 (63.3%)	353 (36.7%)	
Hypertension			
Hypertension	375 (54.7%)	310 (45.3%)	<0.001
No hypertension	333 (70.3%)	141 (29.8%)	
Hyperlipidemia			
Hyperlipidemia	252 (55.9%)	199 (44.1%)	0.004
No hyperlipidemia	456 (64.4%)	252 (35.6%)	
Statins			
Statin use	208 (51.0%)	200 (49.0%)	<0.001
No statin use	500 (66.6%)	251 (33.4%)	

*Chi-square test.
**BMI values were missing for 34 subjects.

significant: methadone vs hydrocodone ($P < 0.001$) and oxycodone vs hydrocodone ($P = 0.002$). Subjects who were obese ($P < 0.001$); who had diabetes ($P < 0.001$), hypertension ($P < 0.001$), or hyperlipidemia ($P = 0.004$); or who took statins ($P < 0.001$) were more likely to be androgen deficient than subjects not having these risk factors (Table 3).

Multivariable Analysis

Our multivariable analysis included 1,128 subjects. Codeine was not included in the multivariable analysis because we present dose in terms of odds per 10 mg MSE, and the maximum dose for codeine in this study was 1.8 mg MSE. We therefore could not calculate odds ratios over this dose range for these subjects.

Opioids

Results for each opioid are presented with reference to hydrocodone, because the bivariate results indicated that subjects using hydrocodone were least likely to be androgen deficient; moreover, it was the largest group. Fentanyl (OR 25.73, CI 2.82–234.97), methadone (OR 7.33, CI 3.29–16.33), and oxycodone (OR 3.15, CI 1.87–5.33) were all associated with higher odds of androgen deficiency than hydrocodone (Table 4). The odds ratio for fentanyl use is high; however, because there were only 13 subjects using fentanyl, the confidence interval is wide, indicating that the odds ratio estimate is not stable. Morphine was also associated with elevated odds of androgen deficiency compared to hydrocodone (OR 2.40, CI 0.92–6.28); however, this result was not statistically significant.

Dose

Dose and opioid were found to have significant interaction; that is, the effect of dose differed depending on the individual opioid. Therefore, the odds of androgen deficiency for each 10 mg increase in dose are reported separately for each opioid (Table 4). Higher dose was associated with increased odds of androgen deficiency among subjects taking hydrocodone (OR 1.18, CI 1.09–1.28) or oxycodone (OR 1.01, CI 1.00–1.02). Dose did not reach statistical significance among morphine users; however the results suggest an association between increased dose and androgen deficiency in these subjects (OR 1.05, CI 0.99–1.11).

Comorbidities

Obesity was a significant contributor to androgen deficiency, as was age $\geq$ 50 plus the presence of two or more of the comorbidities diabetes, hypertension, and hyperlipidemia (Table 4).

Oxycodone

Oxycodone is the only opioid in this study that was used both in short-acting (IR) and long-acting (ER) formulations. Of the 127 subjects on oxycodone, 72 were taking short-acting oxycodone only, 22 were taking long-acting oxycodone only, and 33 were on both long-acting and short-acting oxycodone (Table 1). Androgen deficiency was present in 32 (44.4%) subjects on short-acting oxycodone, in 22 (50.0%) subjects on long-acting oxycodone, and in 21 (63.6%) subjects on both long-acting and short-acting oxycodone.

Table 4 Adjusted odds ratios for androgen deficiency

	Odds ratio	95% Confidence interval
Opioid (referent: Hydrocodone)		
Fentanyl	**25.73**	**2.82–234.97**
Hydromorphone	0.22	0.00–65.96
Methadone	**7.33**	**3.29–16.33**
Morphine	2.40	0.92–6.28
Oxycodone	**3.15**	**1.87–5.33**
Effect of dose (per 10 mg MSE)		
Fentanyl	0.96	0.88–1.03
Hydrocodone	**1.18**	**1.09–1.28**
Hydromorphone	1.34	0.61–2.94
Methadone	0.99	0.97–1.02
Morphine	1.05	0.99–1.11
Oxycodone	1.01	1.00–1.02
Obese (referent: not obese)		
Obese	**2.21**	**1.69–2.89**
Missing	1.33	0.60–2.95
Number of conditions by age* (referent: 0 conditions, < 50 years old)		
0 conditions, age ≥ 50	0.84	0.50–1.41
1 condition, age < 50	1.38	0.85–2.24
1 condition, age ≥ 50	1.43	0.94–2.19
2 conditions, age < 50	1.31	0.66–2.61
2 conditions, age ≥ 50	**1.98**	**1.29–3.04**
3 conditions, age < 50	1.91	0.70–5.18
3 conditions, age ≥ 50	**2.91**	**1.68–5.05**

MSE = morphine standardized equivalent dose.
*The number of conditions is a count of the number of comorbidities present (diabetes, hypertension, hyperlipidemia) stratified by age < 50 years and age ≥ 50 years.
Statistically significant values are shown in **bold**.

We assessed the association between duration of action and androgen deficiency in the 127 subjects on oxycodone (Table 5). As in previous analyses, we assessed the odds among subjects on long-acting oxycodone (either long-acting only or long-acting plus short-acting for breakthrough pain) compared with subjects on short-acting oxycodone only. The odds ratio for duration of action did not reach statistical significance (OR 3.09, 95% CI 0.95–9.99); however, it is suggestive of an association. Similarly, for subjects on short-acting oxycodone, the odds of androgen deficiency increased with each 10-mg increase in dose (OR 1.14, 95% CI 0.99–1.30), but also did not reach significance. Obesity among this population was associated with androgen deficiency (OR 2.64, 95% CI 1.12–6.23), as it was in the larger analysis.

Discussion

Elucidating the mechanism involved in opioid suppression of testosterone has proven challenging. The results

Table 5 Adjusted odds ratios for androgen deficiency in patients taking oxycodone

	Odds ratio	Confidence interval
Duration of action		
Long (referent: short)	3.09	0.95–9.99
Dose (MSE)		
10-mg increase, short duration	1.14	0.99–1.30
10-mg increase, long duration	1.00	0.99–1.01
Obese (referent: not obese)		
Obese	**2.64**	**1.12–6.23**
Missing BMI values	6.17	0.53–71.60
Number of conditions by age* (referent: 0 conditions, < 50 years old)		
0 conditions, ≥ 50	1.99	0.47–8.36
1 condition, < 50	1.15	0.28–4.67
1 condition, ≥ 50	1.40	0.43–4.59
2 conditions, < 50	1.39	0.14–14.06
2 conditions, ≥ 50	2.54	0.74–8.77
3 conditions, < 50	2.07	0.09–46.03
3 conditions, ≥ 50	3.21	0.44–23.51

MSE = morphine standardized equivalent dose.
*The number of conditions is a count of the number of comorbidities present (diabetes, hypertension, hyperlipidemia) stratified by age < 50 years and age ≥ 50 years.
Statistically significant values are shown in **bold**.

of some previous studies have led to speculation that the suppression of testosterone is dose related [20,21], but other studies have failed to show this consistently. Very small studies have shown rates of androgen deficiency that differ between opioids, but the results have generally been descriptive only [22]. One study found that methadone was more suppressive than heroin [23,24]; another reported that morphine appeared to be more suppressive than hydromorphone when used intrathecally [25], but the study was too small to show significance. Our previous work examined opioids classified as either long-acting or short-acting and found that long duration of action was associated with a higher odds ratio of androgen deficiency than equipotent doses of short-acting opioids [8,9]. The opioids in these groups were varied and structurally diverse, and it was not clear whether a specific subset of these opioids was driving the results.

It is important to look at opioids individually because differences in structure, lipophilicity, or other factors might differentially affect the hypothalamic-pituitary-gonadal axis, leading to greater or lesser testosterone suppression. Morphine, codeine, hydrocodone, hydromorphone, and oxycodone are all structurally similar phenanthrene opioids but in this study are associated with widely

different odds of androgen deficiency. Fentanyl and methadone are both lipophilic drugs with large volumes of distribution, and both were associated with high odds of androgen deficiency when compared to the less lipophilic hydrocodone. However, the explanation that lipophilic opioids may be more strongly associated with androgen deficiency seems inadequate, because oxycodone in short-acting form appears to differ from its long-acting but equally lipophilic form in terms of association with androgen deficiency. Neither structure nor lipophilicity seems to provide an adequate explanation for the androgen suppression seen with these drugs.

Our findings show that the highest odds of androgen deficiency are associated with opioids that maintain the most stable serum drug levels. Transdermal fentanyl, which is designed to maintain a very steady serum drug level, has the highest odds ratio, followed by methadone, with an elimination half-life between 8 and 59 hours. Oxycodone ER and morphine ER, both 12-hour formulations, showed similar results to each other. Subjects on hydrocodone and codeine, two short-acting opioids, were least likely to be androgen deficient. The key issue thus may not be inherent properties of any one drug, but the way that the drug or formulation maintains serum drug levels. Because testosterone in men is produced in a pulsatile fashion periodically throughout every 24-hour cycle, we have hypothesized that the nadirs in drug level that occur more frequently between doses of short-acting opioids may allow some testosterone to be produced during these nadirs, which may be sufficient to maintain normal testosterone levels. By contrast, drugs that maintain constant serum levels may suppress testosterone production more completely.

Our previous study showed that dose was more strongly associated with androgen deficiency among men using short-acting opioids than among those using long-acting opioids. This could be explained because as short-acting doses increase, either the time between doses decreases (more frequent dosing) leading to fewer nadirs or the peak serum levels increase (larger doses taken) leading to a higher serum drug level at the nadir. Either of these scenarios could produce drug levels where nadirs are inadequate to allow testosterone production. This analysis further supports the relationship between dose and androgen deficiency among men using short-acting opioids. It is possible that dose may be relevant up to some threshold and then cease to have additional effects. If this is the case, then it, too, would be consistent with our nadir hypothesis.

Androgen deficiency is associated with several comorbidities, most notably obesity, hypertension, hyperlipidemia, and diabetes. It had been assumed that these conditions lead to androgen deficiency, but more recent work has called this simple relationship into question. It may be that androgen deficiency at least partially causes, rather than is simply the result of, the development of these comorbidities [17,26]. The relationship may also be more complex, leading to a feedback

pattern wherein obesity leads to lower testosterone, which feeds back to reduce lean muscle mass, which leads to additional obesity. We found that men age 50 or above having at least two comorbidities (hyperlipidemia, diabetes, or hypertension) were more likely to have androgen deficiency. Additionally, obesity was independently associated with androgen deficiency. However, we were unable to elucidate in our subjects whether any of these relationships were bidirectional. When we controlled for these conditions, the role of opioids in androgen deficiency remained strong.

While it is outside the scope of this paper to discuss the diagnosis and treatment of androgen deficiency in the opioid using population, it is interesting to note that testosterone screening is not yet the standard of care in many places. We suggest that testosterone tests be performed before commencement of opioid therapy or modification to existing opioid therapy in order to identify androgen deficiency subsequent to opioid use.

Strengths and Limitations

This study is a retrospective cohort study. Because testosterone levels are not yet routinely followed as part of opioid monitoring, this particular cohort was likely symptomatic, which may have resulted in an overestimation of the prevalence of androgen deficiency. It is also possible that some men may have experienced a significant lowering of testosterone levels due to opioids but remained in the normal range, in which case our results would have underestimated the effect size.

While it has been well established that opioids affect the hypothalamic-pituitary-gonadal axis, it is possible that pain or the sequelae of chronic pain may contribute to low androgen levels in men, and this may have been a confounder in this study.

KPNC is a closed system, and more than 90% of our patients receive their medications through our pharmacy, but we cannot be certain that patients were taking their medications as prescribed. Because of the nature of opioids, however, most people who are prescribed opioids chronically do take them at regular intervals to maintain analgesia as well as to avoid withdrawal.

The overall sample size for our study was large, particularly for a study assessing the relationship between opioids and androgen deficiency. Combined with our integrated system of utilization, laboratory, and pharmacy data, this large sample size afforded us power to assess outcomes across specific opioids. However, the stringent inclusion criterion of using only one opioid in order to isolate the effect of individual drugs resulted in the exclusion of many subjects on long-acting opioids who used one opioid around the clock and another for breakthrough pain. Because of this, we were most likely underpowered in some comparisons, although the

results seem to confirm that duration of action is the driving factor in androgen deficiency.

Conclusion

Transdermal fentanyl, methadone, and oxycodone (long and short-acting formulations combined) were associated with higher odds of androgen deficiency when compared to hydrocodone. Higher dose was associated with increased odds of androgen deficiency only in hydrocodone and oxycodone. Age $\geq$ 50 years and the presence of two or three of the comorbidities diabetes, hypertension, and hyperlipidemia was associated with androgen deficiency; however, this association was not as strong as the association between fentanyl, methadone, or oxycodone and androgen deficiency.

When opioid risk is discussed it is almost always in terms of abuse, addiction, or diversion. There is growing evidence, however, of other medical risks that must be taken into consideration when choosing to prescribe. Androgen deficiency is common among men who use opioids, and the strength of the association seems to vary by drug. The convenience of the fentanyl patch must be looked at against its particularly high incidence of androgen deficiency in men. Similarly, the low cost of methadone should be weighed against the known risk of QT prolongation as well as its substantial association with androgen deficiency. Short-acting opioids lack the convenience of long-acting formulations but have never been shown to have an increased risk of addiction, misuse, or diversion compared with long-acting opioids despite beliefs to the contrary [4,27,28]. Short acting opioids may represent less risk although this effect may diminish as dose increases.

When making opioid prescribing decisions, all risks should be weighed against benefits for each patient; understanding these risks can help better inform prescribing decisions.

Acknowledgments

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