Chronic Opioid Use and Hypogonadism: Establishing a Dose-Response Relationship

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Introduction

The negative sequela of chronic opioid use on the endocrine system are frequently unrecognized. Opioid-Induced Androgen Deficiency (OPIAD) related to chronic long-acting opioid use can be a significant detriment to both patient quality of life as well as the health care system. Examining the dose-response relationship between opioids and hypogonadism could shape future clinical guidelines for the diagnosis and management of OPIAD.

Methods

An IRB-approved retrospective matched case-control study was performed on 357 men (94 cases, 263 controls) aged 18-80 years old. Selected men carried a diagnosis of chronic opioid use, defined as continuous opioid use longer than 3 months. Exclusion criteria included: having a diagnosis of hypogonadism before start of chronic opioid use, a history of Klinefelter syndrome, chromosomal abnormalities, cryptorchidism, varicocele, myotonic dystrophy, mumps infection, radiation to the testes, testicular torsion, long-term corticosteroid use, prostate cancer, or known endocrine disorder.

Controls selection: each patient in the hypogonadism group was matched to pools of patients by age, race, and body mass index (BMI) that carried no diagnosis of hypogonadism or low testosterone. Matching was aimed for a 1:4 ratio (for each case up to 4 matched controls, if available). Morphine equivalent daily dose (MEDD) data was collected from the EPIC electronic health record (EHR).

Observed prevalence of hypogonadism at ranges of MEDD were calculated. The association between hypogonadism and the MEDD was evaluated by conditional logistic regression with linear term of continuous MEDD. Accounting of potential confounders age, BMI, and ethnicity was done by matching. Non-linear association of MEDD with hypogonadism was assessed with restricted cubic splines. Analyses were carried in SAS STAT 14.2.

Results

A significant linear association between max morphine equivalent daily dose (MEDD) and the odds of developing hypogonadism (p=0.0008) in men with chronic use of long-acting opioids was observed, with an odds ratio of 1.44 with 95% CI (1.16,1.78) by 100 units difference in max MEDD. For sets of patients receiving a differential of 100 units of max MEDD, the chances of developing hypogonadism in the higher max MEDD group are increased by 44% (16%, 78%). There is a nonlinear association of MEDD with the odds of hypogonadism status (p=0.035).

Table 1: Prevalence Table

	Hypogonadism		Controls		Total
MEDD	N	%	N	%	
0-99	21	15.6	114	84.4	135
100-199	38	27.1	102	72.9	140
200-299	22	41.5	31	58.5	53
300-499	5	35.7	9	64.3	14
500-800	7	50.0	7	50.0	14
	93		263		356

Table 1: Prevalence (table) of hypogonadism seems to vary with MEDD, ranging from 15% (MEDD<100) to 50% (MEDD between 500 to 800).

Figure 1: Estimated Hypogonadism Probability

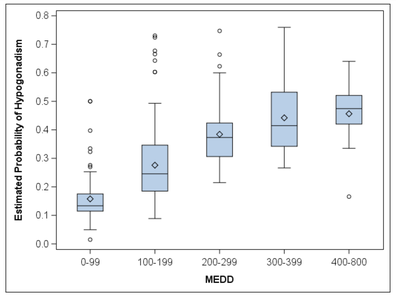

Figure 1: This figure shows estimated probabilities of hypogonadism for patients at various ranges of MEDD. Plateau of probabilities at MEDD in 500-800 range are based on limited sample size (N=14).

Figure 2: Expected Hypogonadism Probability

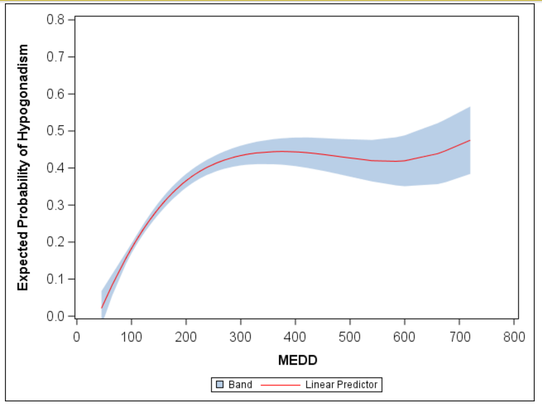

Figure 2: This figure shows the estimated expected probability of hypogonadism as a function of continuous MEDD. Band represents confidence interval of expected probability. Wider confidence intervals at ends of MEDD reflect smaller sample sizes; thus less certainty about estimated probability of hypogonadism.

Conclusions

Findings from this study require replication in other clinical settings.

If current findings are replicated, demonstrating a dose-response relationship between chronic opioid use and hypogonadism in men, there should be an increasing index of suspicion for the development of OPIAD and hypogonadism in patients receiving higher dose chronic opioid therapy. This higher index of suspicion could lead to earlier recognition of symptoms, increase the positive predictive value of diagnostic laboratory tests, and potentially assist in the formation clinical guidelines for the diagnosis and management of OPIAD in future prospective studies.

References

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