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Arrhythmia Associated with Buprenorphine and Methadone Reported to the Food and Drug Administration

David P Kao, MD[1], **Mark CP Haigney, MD**[2], **Philip S Mehler, MD**[1,3], and **Mori J Krantz, MD**[1,4]

[1]University of Colorado School of Medicine, Aurora CO

[2]Uniformed Services University, Bethesda MD

[3]Department of Patient Safety and Quality, Denver Health, Denver CO

[4]Denver Health, Cardiology Division, Denver CO

Abstract

Aim—To assess the relative frequency of reporting of adverse events involving ventricular arrhythmia, cardiac arrest, QTc prolongation, or torsade de pointes to the US Food and Drug Administration (FDA) between buprenorphine and methadone.

Design—Retrospective pharmacoepidemiologic study

Setting—Adverse drug events spontaneously reported to the FDA between 1969-June 2011 originating in 196 countries (71% events from the US).

Cases—Adverse event cases mentioning methadone (n=14,915) or buprenorphine (n=7,283) were evaluated against all other adverse event cases (n= 4,796,141).

Measurements—The primary outcome was the composite of ventricular arrhythmia or cardiac arrest. The secondary outcome was the composite of QTc prolongation or torsade de pointes. The proportional reporting ratio (PRR) was used to identify disproportionate reporting defined as a PRR>2, $\chi 2$ error>4, with ≥3 cases.

Findings—There were 132 (1.8%) ventricular arrhythmia/cardiac arrest and 19 (0.3%) QTc prolongation/torsade de pointes cases associated with buprenorphine compared with 1729 (11.6%) ventricular arrhythmia/cardiac arrest and 390 (2.6%) QTc prolongation/torsade de pointes cases involving methadone. PRRs associated with buprenorphine were not significant for ventricular arrhythmia/cardiac arrest (1.1 95% confidence interval (CI) 0.9–1.3, $\chi 2=1.2$) or QTc prolongation/torsade de pointes (1.0 95% CI 0.7–1.9, $\chi 2=0.0006$), but were for methadone (7.2 95% CI 6.9–7.5, $\chi 2=9160$; 10.6 95% CI 9.7–11.8, $\chi 2=3305$, respectively).

Conclusion—In spontaneously reported adverse events, methadone is associated with disproportionate reporting of cardiac arrhythmias, whereas buprenorphine is not. Although these findings probably reflect clinically relevant differences, a causal connection cannot be presumed

Address for correspondence and reprint requests: David Kao, MD, University of Colorado School of Medicine, 12700 E 18th Ave Box B-139, Aurora, CO 80045, David.Kao@ucdenver.edu, Phone: 303-724-8308 Fax: 720-863-0940.

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and disproportionality analysis cannot quantify absolute risk per treatment episode. Population-based studies to definitively quantify differential incidence rates are warranted.

Keywords

buprenorphine; methadone; torsade de pointes; QTc prolongation; pharmacovigilance

INTRODUCTION

As of January 2013, federal regulations restrict United States opioid treatment programs to only two opioid-agonist therapies approved by the Food and Drug Administration (FDA): methadone and buprenorphine. [1] A third medication, the methadone derivative levacetylmethadol, was withdrawn from both European Union and United States markets due to reports of ventricular arrhythmia including torsade de pointes. [2] Methadone and buprenorphine are both effective in reducing illicit opioid use. However, a recent Cochrane Review [3] and an independent systematic review [4] both noted greater treatment retention and lower cost associated with methadone compared with buprenorphine therapy when using a flexible dosing strategy. Flexible dosing is more common in clinical practice than fixed dosing and permits the dose to be individualized to each patient instead mandating a standard fixed dose. Increasingly, medication-assisted treatment of opioid dependence is delivered in the primary care setting. There are relatively few data comparing methadone and buprenorphine outside of specialized opiate treatment centers, and the implications of unstructured medication-assisted treatment of opioid dependence for prevention of treatment-related adverse events remain unknown. As more patients are treated in the primary care setting, differences in drug safety profiles favoring buprenorphine might be important when selecting a medication for a given patient.

Methadone and buprenorphine both block the cardiac potassium ion current encoded by the human Ether-à-go-go gene (hERG) *in vitro*, which can result in delayed cardiac repolarization. Drug-induced blockade of the hERG channel *in vivo* manifests as prolongation of the heart rate-corrected QT (QTc) interval and may result in torsade de pointes, a potentially lethal ventricular arrhythmia. [5] Unlike methadone, *in vitro* data suggest buprenorphine has little impact on the hERG channel at maximum serum concentrations and therefore QTc prolongation *in vivo* should be significantly less. [6] Accordingly, guideline recommendations suggest buprenorphine is a potentially safe alternative for patients who develop QTc prolongation during methadone treatment. [7] However, a recent study of high-dose transdermal buprenorphine demonstrated a significant increase in mean QTc interval and led to a boxed warning in the FDA-approved label. [8] In a randomized trial comparing buprenorphine, methadone, and levacetylemethadol, buprenorphine was associated with a numerical but statistically non-significant increase in QTc interval, whereas methadone and levacetylmethadol both led to significant QTc prolongation. [9] Furthermore, epidemiologic data from 1994–1998 in France suggest that sudden death rates were lower in buprenorphine-maintained patients relative to methadone, though the study may have been confounded by decreased severity of addiction among buprenorphine-treated patients. [10] Therefore, the clinical importance of QTc prolongation observed with transdermal buprenorphine remains uncertain.

The goal of this study was to determine whether US pharmacovigilance data suggest differences in cardiac safety between methadone and buprenorphine. To evaluate this, we performed the following analyses:

1. We summarized descriptive statistics of methadone and buprenorphine-associated adverse events including rates of adverse events, and outcomes.
2. We compared signals of disproportionate reporting for the composite of ventricular arrhythmia and cardiac arrest as well as the composite of QTc-prolongation and torsade de pointes between methadone and buprenorphine.

We hypothesized that buprenorphine would be associated with proportionately lower ventricular arrhythmia reporting in this large pharmacovigilance database signifying a more favorable cardiac safety profile of buprenorphine relative to methadone.

METHODS

Design

This was a retrospective, descriptive pharmocoepidemiologic study conducted under an exemption from the Colorado Multiple Institutional Review Board.

Cases

Publicly available data from the Spontaneous Reporting System (January 1969–December 1997) were merged with Legacy Adverse Event Reporting System data (November 1997–June 2011) to make a combined dataset spanning January 1969–June 2011. [11] Entities reporting adverse events to the FDA include patients, providers, legal representatives, and pharmaceutical companies.

Measurements

The primary outcome was the composite of ventricular arrhythmia or cardiac arrest. Secondary outcomes were the composite of QTc prolongation or torsade de pointes and torsade de pointes alone. The proportional reporting ratio (PRR) was used to identify disproportionate reporting of the primary and secondary outcome.

Data methods

Because multiple reports may describe a single adverse drug reaction, we quantified unique cases as determined by the FDA rather than quantifying individual reports for all measures to minimize redundant counting. This practice has been incorporated in the latest version of the FDA Adverse Event Report System for data collected after 2012. [12; 13] Drug ingredients were identified using exact, then partial-string matching to entities in the Drugs@FDA database, [13] and cases involving methadone (‘METHADONE HYDROCHLORIDE’) or buprenorphine (‘BUPRENORPHINE’, ‘BUPRENORPHINE HYDROCHLORIDE’) were identified. All buprenorphine and methadone cases were included irrespective of reported indication (pain vs. opioid dependency). Adverse drug reactions were categorized from primary submitted reports by FDA staff using Coding Symbols for a Thesaurus of Adverse Reactions Terms (COSTART, 1969–1997) or the

Medical Dictionary for Regulatory Activities (MedDRA, 1997-present, Northrop Grumman, Falls Church, Virginia). [14] All COSTART terms were mapped to MedDRA Preferred Terms using standard definitions. MedDRA terms of interest were QTc prolongation ('ELECTROCARDIOGRAM QT PROLONGED', 'ELECTROCARIOGRAM QT CORRECTED INTERVAL PROLONGED', 'LONG QT SYNDROME'), torsade de pointes ('TORSADE DE POINTES'), or ventricular arrhythmia and cardiac arrest ('VENTRICULAR ARRHYTHMIAS AND CARDIAC ARREST'). QTc prolongation and torsade de pointes terms were aggregated as were ventricular arrhythmia and cardiac arrest terms as described previously. [12] The roles of buprenorphine and methadone in each case were classified as 'primary suspect', 'secondary suspect', 'concomitant', or 'interacting' by the reporting entity at the time of reporting, and the proportion of each role was quantified for each drug. Data integration was performed using MySQL Server, version 5.5.24 (Oracle Corporation, Redwood Shores, California).

Statistical analysis

Age distributions were compared using the Mann-Whitney U test due to a bimodal age distribution with peaks at birth and age ~40 years for both methadone and buprenorphine cases. Spontaneously reported databases are subject to many limitations including inability to establish definitive rates of exposure, redundancy in reporting, inaccuracy of reported data, reporting bias, and conflicting reports. [15] For these reasons, analysis for signals of disproportionate reporting using either frequentist methods (2×2 tables) or Bayesian decision frameworks are used to identify possible adverse drug event signals in spontaneously reported databases. [16] We calculated the proportional reporting ratio (PRR), a frequentist measure, and corresponding 95% confidence intervals (CI) for the two drugs to identify disproportionate reporting of specific adverse drug reactions as previously described. [12] The PRR measures strength of association between a drug and a specific adverse reaction and is analogous to an odds ratio. A higher PRR value suggests that reporting of the reaction of interest is disproportionately elevated relative to all other reported adverse reactions for that drug. Although each signal of disproportionate reporting method uses different assumptions, direct comparison shows similar performance between the PRR method and Bayesian methods when there are > 3 adverse events of interest, as was the case for all drug-adverse event associations in the present analysis. The PRR has been identified as a valid approach to screening for signals of disproportionate reporting in the FDA guidance on pharmacovigilance and pharmacoepidemiologic assessment, [17] and the PRR has been used by both the European Medicines Agency (Eudravigilance system) [18] and the United Kingdom's Yellow Card Scheme. [19]

The PRR is calculated by dividing the fraction of reports involving the reaction of interest for a given drug by the fraction of reports involving the reaction of interest for all other drugs using the following formula: $PRR = [\text{Event of interest}_{Drug}/\text{All events}_{Drug}]/[\text{Event of interest}_{\text{All other drugs}}/\text{All events}_{\text{All other drugs}}]$. [19] P-values are not used to assess the significance of PRRs, so the χ^2 statistic was calculated as an alternative measure of association between the drug of interest and the adverse event of interest to assist in determining significance of each PRR findings (1 degree of freedom). [18] A PRR was considered significantly elevated according to standard empirically derived criteria used by

multiple national agencies and pharmacovigilance researchers: 1) PRR ≥ 2, 2) $\chi^2 \geq 4$, and 3) at least 3 unequivocal reports in the database. [19–22] Analyses were performed using the R statistical package (Version 3.0.2, The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

A total of 4,418,215 cases from 1969–2011 were evaluated of which 7,283 involved buprenorphine and 14,915 involved methadone. Characteristics of methadone and buprenorphine cases are summarized in Table 1. Mean age was similar between methadone and buprenorphine cases as was gender (54.0% female vs. 54.4% male where reported), although gender was reported in 81.5% buprenorphine cases compared to only 61.8% of methadone cases. Death was reported in 857 (11.8%) of buprenorphine cases and 5813 (39.0%) of methadone cases. Ventricular arrhythmia or cardiac arrest was reported in 1.8% of buprenorphine cases compared with 11.6% of methadone cases. Similarly, 0.3% of buprenorphine cases reported QTc prolongation/torsade de pointes compared with 2.6% of methadone cases. Torsade de pointes was reported in 0.1% of buprenorphine cases compared with 1.7% of methadone cases.

The suspected role of buprenorphine and methadone in cases of ventricular arrhythmia and cardiac arrest, QTc prolongation/torsade de pointes and torsade de pointes alone are summarized in Table 2. Buprenorphine was reported as the primary or secondary suspect in significantly fewer ventricular arrhythmia and cardiac arrest cases ($p<0.001$). Buprenorphine was also associated with fewer cases of QTc prolongation/torsade de pointes cases and torsade de pointes alone compared with methadone ($p<0.001$ for both). The 10 cases of torsade de pointes involving buprenorphine are described in Table 3. In all 10 cases, buprenorphine was reported as a concomitant drug, and at least one other known QTc prolonging medication was reported. Methadone and buprenorphine were reported concomitantly in 124 cases. When buprenorphine and methadone were co-reported, the frequency of cases mentioning torsade de pointes was higher than for either buprenorphine or methadone alone.

Event counts and corresponding PRRs for cardiac arrhythmia events associated with buprenorphine and methadone are found in Table 4. The PRRs for buprenorphine were not significant for ventricular arrhythmia and cardiac arrest, QTc prolongation/torsade de pointes or torsade de pointes alone, whereas all PRRs were significant for methadone. The PRR for the combination of methadone and buprenorphine was higher than for methadone alone for QTc prolongation/torsade de pointes and for torsade de pointes alone, but lower for ventricular arrhythmia and cardiac arrest.

Given differing dates of market availability for methadone (1940s) and buprenorphine (1982), a sensitivity analysis was performed excluding all methadone cases reported prior to the first FDA submission of buprenorphine-associated adverse events. All arrhythmia PRRs were found to be higher for methadone with no change in buprenorphine PRRs.

DISCUSSION

This study found proportionately fewer reports to the FDA of ventricular arrhythmia-associated adverse events associated with buprenorphine relative to methadone. Furthermore, buprenorphine was less likely to be identified as a primary or secondary suspect in ventricular arrhythmia cases. In the 10 cases of torsade de pointes associated with buprenorphine between 1982 and 2011, another established QTc prolonging medication was reported concurrently in every case. Although the formal cutoff of a significant PRR is > 2, it has been observed that a PRR of 3–5 is more suggestive of a clinically meaningful signal. [19] All PRRs for ventricular arrhythmia and methadone alone were > 7. By contrast, there was no signal of disproportionate reporting for buprenorphine either in the broader category of ventricular arrhythmia and cardiac arrest or in association with the more specific arrhythmia diagnosis of torsade de pointes (maximum PRR 1.6). Our population-based findings are consistent with *in vitro* studies demonstrating that blockade of the cardiac hERG channel was nearly an order of magnitude higher relative to expected maximal serum concentrations for buprenorphine compared with methadone. [6] Taken together, there appears to be a wider margin of safety for buprenorphine than methadone with respect to arrhythmia liability. This may be an important consideration given the increasing number of patients being treated for opioid dependence in the primary care setting.

Buprenorphine and Opioid Mortality

Reductions in death risk associated with buprenorphine have been reported, but the mechanism is unclear. A 79% decline in “opiate overdose deaths” was observed in France with the introduction of buprenorphine as opioid maintenance therapy in 1995, [10] and this decline has been attributed primarily to the partial opioid agonist properties of buprenorphine that limit central nervous system depression. Similarly, a recent report from the Centers for Disease Control found that during 2009, methadone was associated with mortality 50–100 times higher than buprenorphine when assessed as rate of death per 100 kg of medication prescribed. [23] Buprenorphine is a partial opioid agonist and presumably has a lower overdose liability, but the results of the current study suggest that a decrease in ventricular arrhythmia could have also contributed to the lower observed mortality compared to methadone. Further studies should attempt to isolate these effects.

The assessment of comparative cardiac safety between agents must be viewed in the context of comparative clinical efficacy with regard to illicit opioid abuse. Although the two agents appear equally effective in reducing heroin use, meta-analyses indicate that methadone is associated with better retention than buprenorphine. This superiority was manifest in flexible dosing strategies common in clinical practice, even when buprenorphine was also administered in structured opioid treatment programs. [3; 4] However, buprenorphine is increasingly prescribed using take-home dosing or outside treatment programs, and the implications of these new practice patterns for overall adherence to methadone compared with buprenorphine are not well established. Participation in opioid treatment programs provides increased opportunity to screen for presyncope, syncope, or QTc prolongation, so as to make dose adjustments that reduce the magnitude of QTc prolongation. [24] Therefore from a cardiac safety perspective methadone may be better suited to patients requiring more

structured care whereas buprenorphine may be more appropriate for those being treated in a less supervized fashion.

Transdermal Buprenorphine and QTc Prolongation

The present study does not exclude the possibility that a transdermal formulation of buprenorphine might manifest a higher arrhythmia liability relative to oral or sublingual delivery systems. Only one study addresses the effect of a transdermal buprenorphine patch (Butrans®) on QTc-interval prolongation. [8] This double-blind, randomized, placebo-controlled, parallel-group, dose-escalating, study involved 132 healthy subjects aged 18 to 55 years. A dose of 40 mcg/hour prolonged the mean QTc interval by a maximum of 9.2 (90% CI 5.2–13.3) ms over the course of the study. Although the magnitude of the QTc interval change from baseline was modest and occurred at twice the maximum approved dose of Butrans®, the 90% CI exceeded the point estimate of the impact of methadone on QTc-interval prolongation (12.3±23 ms) at 6 months. [25] The Butrans® study raises concern regarding the potential arrhythmia liability of buprenorphine, but our current pharmacovigilance analysis suggests that at present, there is no significant signal of ventricular arrhythmia associated with buprenorphine products in the US. However, it is remains possible that buprenorphine could induce clinically important QTc prolongation in some patients, particularly when delivered transdermally. The transdermal preparation of buprenorphine was only approved in the US in 2010, and there are currently insufficient pharmacovigilance data to adequately assess disproportionate reporting for QTc prolongation or ventricular arrhythmia with this specific formulation.

Risk of Buprenorphine in Combination with Other Agents

Buprenorphine may potentiate the effects of other hERG blocking agents, and our results suggest that the combination of buprenorphine and methadone may be associated with a higher risk of QTc prolongation/torsade de pointes than methadone alone. Gruber and McKance also found a statistically significant 8.2 ms increase in the QTc interval from baseline among buprenorphine patients receiving highly active antiretroviral therapy. [26] This finding is analogous to a previous study suggesting that the most frequently prescribed concomitant medications among cases of methadone-associated QTc prolongation/torsade de pointes were antiretroviral drugs in patients with human immunodeficiency virus (HIV). [12] This effect could be related either to additive hERG channel blockade or to increased serum drug concentrations resulting from changes in metabolism. [26; 27] An estimated 10–15% of all heroin users are HIV-positive, [28–30] and medication-assisted opioid treatment programs provide structure including directly administered treatment that increase adherence to antiretroviral therapy. [31; 32] Therefore HIV-positive opioid addicts on antiretroviral therapy may represent an important subgroup of patients at higher risk of cardiac arrhythmia due to QTc prolongation. Finally, genetic mutations of either cardiac ion channels or cytochromes P450 may also increase the likelihood of QTc prolongation or torsade de pointes when exposed to hERG channel blockers. [33] Taken together, these findings suggest that providers caring for these vulnerable populations should be vigilant when co-administering either methadone or buprenorphine with other QTc prolonging drugs including psychotropics and antiretrovirals or in the setting of congenital long QT syndrome.

Limitations

We acknowledge several limitations, many of which are inherent to spontaneous reporting databases. Reports are voluntary, and the actual incidence of each adverse reaction cannot be inferred from the present study. Spontaneous reports are subject to many sources of bias. Reporting bias due to publicity or perceived severity of reaction is a particular concern, since methadone has received significant notoreity for proarrhythmia for some time. When several adverse reactions occur concurrently, the primary adverse reaction attributable to the drug cannot be definitively identified. Details regarding dose and patient comorbidities were not evaluated due to incomplete reporting to the FDA. In order to maximize specificity in identifying adverse event cases of interest, we used string matching between verbatim drug names from adverse event reports and entries in the Drugs@FDA database. We did not consider misspelling, formatting errors, or punctuation marks. Consequently, some cases involving methadone or buprenorphine may not have been identified and reporting rates may be underestimated. Methadone received marketing approval prior to buprenorphine, which could magnify the number of methadone-associated adverse event reports. However, 12,760 of 14,915 (85.5%) methadone reports occurred while the drugs were co-marketed, and findings were very similar when analysis was limited to the time during which the drugs were co-marketed.

Prescription volume is not part of the FDA surveillance system, which prevents calculation of absolute reporting rates and necessitates using signals of disproportionate reporting like the PRR. Although such measures are generally less biased than comparisons of raw report counts, the PRR is subject to a number of limitations. First, the PRR is especially vulnerable to confounding factors when the number of reports is low (<10). [34] In addition, the presence of a very strong signal between a drug and an adverse event can affect PRRs for the same reaction with other drugs. [19] It is also difficult to adjust for confounders such as age, gender, and temporal factors that could influence results. For example, immediately after marketing approval of a medication, a higher volume of adverse event reporting is expected (the Weber effect), [35] which could affect the PRR. [36] Although the pharmacovigilance findings are robust by regulatory standards, they cannot account for hidden bias and confounding, [16] which can only be addressed by a randomized trial. Given the rarity of ventricular arrhythmia events, however, an adequately powered trial would require a very large number of patients to detect differences in arrhythmia events.

CONCLUSION

Buprenorphine is prescribed widely in Europe. Its use is growing in the US through expanded use by waivered outpatient primary care physicians [37] and increased use by opioid treatment programs following the recent federal rule-change giving more flexibility in dispensing take-home buprenorphine. [1] Methadone possesses advantages with respect to cost and patient retention with flexible dosing, but pending direct comparative studies, buprenorphine appears to be a safer therapy than methadone with respect to risk of ventricular arrhythmia (especially torsade de pointes). Therefore, cardiac safety may be an important consideration along with cost, availability, addiction severity, and program retention when individualizing medication-assisted treatment of opioid dependence.

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References

1. Substance Abuse and Mental Health Services Administration (SAMHSA). Opiod drugs in maintenance and detoxification treatment of opiate addiction; Proposed modification of dispensing restrictions for buprenorphine and buprenorphine combination as used in approved opioid treatment medications. Federal Register. 2012; 77:72752–72761. [PubMed: 23227572]
2. US Food and Drug Administration. [cited 2013, Aug 13] Safety alert for ORLAAM (levomethadyl acetate hydrochloride. Medwatch. 2003. Available from: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm153332.htm, archived at http://www.webcitation.org/6VLVuCuUg.
3. Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev. 2014; 2:CD002207. [PubMed: 24500948]
4. Connock M, Juarez-Garcia A, Jowett S, Frew E, Liu Z, Taylor RJ, et al. Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation. Health Technol Assess. 2007; 11:1–171. iii–iv. [PubMed: 17313907]
5. Roden DM, Woosley RL, Primm RK. Incidence and clinical features of the quinidine-associated long QT syndrome: implications for patient care. Am Heart J. 1986; 111:1088–1093. [PubMed: 3716982]
6. Katchman AN, McGroary KA, Kilborn MJ, Kornick CA, Manfredi PL, Woosley RL, Ebert SN. Influence of opioid agonists on cardiac human ether-a-go-go-related gene K(+) currents. J Pharmacol Exp Ther. 2002; 303:688–694. [PubMed: 12388652]
7. Martin JA, Campbell A, Killip T, Kotz M, Krantz MJ, Kreek MJ, et al. QT interval screening in methadone maintenance treatment: report of a SAMHSA expert panel. J Addict Dis. 2011; 30:283–306. [PubMed: 22026519]
8. Purdue Pharma, Inc. [cited 2014, Jun 6] Prescribing information: BUTRANS (buprenorphine) transdermal system. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021306s001s003lbl.pdf, archived at http://www.webcitation.org/6VLVR73Qd.
9. Wedam EF, Bigelow GE, Johnson RE, Nuzzo PA, Haigney MC. QT-interval effects of methadone, levomethadyl, and buprenorphine in a randomized trial. Arch Intern Med. 2007; 167:2469–2475. [PubMed: 18071169]
10. Auriacombe M, Franques P, Tignol J. Deaths attributable to methadone vs buprenorphine in France. JAMA. 2001; 285:45. [PubMed: 11150107]
11. FDA/CDER Office of Surveillance and Epidemiology. [cited 2012, Mar 1] The Adverse Event Reporting System (AERS): Latest Quarterly Data Files. Available from: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm082193.htm, archived at http://www.webcitation.org/6VLUVxWqm.
12. Kao D, Bucher Bartelson B, Khatri V, Dart R, Mehler PS, Katz D, Krantz MJ. Trends in reporting methadone-associated cardiac arrhythmia, 1997–2011: an analysis of registry data. Ann Intern Med. 2013; 158:735–740. [PubMed: 23689766]

13. Kao DP, Hiatt WR, Krantz MJ. Proarrhythmic Potential of Dronedarone: Emerging Evidence from Spontaneous Adverse Event Reporting. Pharmacotherapy. 2012; 32:767–771. [PubMed: 22744806]
14. Brajovic, S. MedDRA Use at the FDA; International Conference of Harmonisation of Technical Requiremrents for Registration of Pharmaceuticals for Human Use; 2010. Available from: http://www.ich.org/fileadmin/Public_Web_Site/Training/GCG_-_Endorsed_Training_Events/ASEAN_MedDRA_March_2010/Day_3/Regulatory_Perspective_SBrajovic.pdf, archived at http://www.webcitation.org/6VLUGngEp.
15. Gould AL. Practical pharmacovigilance analysis strategies. Pharmacoepidemiol Drug Saf. 2003; 12:559–574. [PubMed: 14558179]
16. Harpaz R, DuMouchel W, LePendu P, Bauer-Mehren A, Ryan P, Shah NH. Performance of pharmacovigilance signal-detection algorithms for the FDA adverse event reporting system. Clin Pharmacol Ther. 2013; 93:539–546. [PubMed: 23571771]
17. Center for Drug and Evaluation Research, Center for Biologics Evaluation and Research, and Food and Drug Administration. [cited 2014, Jun 6] Good pharmacovigilance practices and pharmacoepidemiologic assessment. Good pharmacovigilance practices and pharmacoepidemiologic assessment. 2005. Available from: http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126834.pdf, archived at http://www.webcitation.org/6VLTfqkL9.
18. EudraVigilance Expert Working Group. Guideline on the use of statistical signal detection methods in the EudraVigilance data analysis system. Guideline on the use of statistical signal detection methods in the EudraVigilance data analysis system. 2006 Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/11/WC500011437.pdf, archived at http://www.webcitation.org/6VLSyD2Hv.
19. Evans SJ, Waller PC, Davis S. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. Pharmacoepidemiol Drug Saf. 2001; 10:483–486. [PubMed: 11828828]
20. Matsushita Y, Kuroda Y, Niwa S, Sonehara S, Hamada C, Yoshimura I. Criteria revision and performance comparison of three methods of signal detection applied to the spontaneous reporting database of a pharmaceutical manufacturer. Drug Saf. 2007; 30:715–726. [PubMed: 17696584]
21. Hauben M, Zhou X. Quantitative methods in pharmacovigilance: focus on signal detection. Drug Saf. 2003; 26:159–186. [PubMed: 12580646]
22. Hochberg AM, Hauben M, Pearson RK, O'Hara DJ, Reisinger SJ, Goldsmith DI, et al. An evaluation of three signal-detection algorithms using a highly inclusive reference event database. Drug Saf. 2009; 32:509–525. [PubMed: 19459718]
23. Centers for Disease Control and Prevention (CDC). Vital signs: risk for overdose from methadone used for pain relief - United States, 1999–2010. MMWR Morb Mortal Wkly Rep. 2012; 61:493–497. [PubMed: 22763888]
24. Katz DF, Sun J, Khatri V, Kao D, Bucher-Bartelson B, Traut C, et al. QTc Interval Screening in an Opioid Treatment Program. Am J Cardiol. 2013; 112:1013–1018. [PubMed: 23820570]
25. Martell BA, Arnsten JH, Krantz MJ, Gourevitch MN. Impact of methadone treatment on cardiac repolarization and conduction in opioid users. Am J Cardiol. 2005; 95:915–918. [PubMed: 15781034]
26. Baker JR, Best AM, Pade PA, McCance-Katz EF. Effect of buprenorphine and antiretroviral agents on the QT interval in opioid-dependent patients. Ann Pharmacother. 2006; 40:392–396. [PubMed: 16507617]
27. Gruber VA, McCance-Katz EF. Methadone, buprenorphine, and street drug interactions with antiretroviral medications. Curr HIV/AIDS Rep. 2010; 7:152–160. [PubMed: 20532839]
28. Keen L, Khan M, Clifford L, Harrell PT, Latimer WW. Injection and non-injection drug use and infectious disease in Baltimore City: differences by race. Addict Behav. 2014; 39:1325–1328. [PubMed: 24837755]
29. Broz D, Wejnert C, Pham HT, DiNenno E, Heffelfinger JD, Cribbin M, et al. HIV infection and risk, prevention, and testing behaviors among injecting drug users -- National HIV Behavioral

Surveillance System, 20 U.S. cities, 2009. MMWR Surveill Summ. 2014; 63:1–51. [PubMed: 24990587]

30. Liebrenz M, Stohler R, Nordt C. Ethnic- and gender-specific differences in the prevalence of HIV among patients in opioid maintenance treatment-a case register analysis. Harm Reduct J. 2014; 11:23. [PubMed: 25130184]
31. Lin C, Cao X, Li L. Integrating antiretroviral therapy in methadone maintenance therapy clinics: Service provider perceptions. Int J Drug Policy. 2014; 25:1066–1070. [PubMed: 24939555]
32. Sorensen JL, Haug NA, Larios S, Gruber VA, Tulsky J, Powelson E, et al. Directly administered antiretroviral therapy: pilot study of a structural intervention in methadone maintenance. J Subst Abuse Treat. 2012; 43:418–423. [PubMed: 23007110]
33. Anchersen K, Hansteen V, Gossop M, Clausen T, Waal H. Opioid maintenance patients with QTc prolongation: congenital long QT syndrome mutation may be a contributing risk factor. Drug Alcohol Depend. 2010; 112:216–219. [PubMed: 20702049]
34. Ahmed I, Thiessard F, Miremont-Salamé G, Haramburu F, Kreft-Jais C, Bégaud B, Tubert-Bitter P. Early detection of pharmacovigilance signals with automated methods based on false discovery rates: a comparative study. Drug Saf. 2012; 35:495–506. [PubMed: 22612853]
35. Wallenstein EJ, Fife D. Temporal patterns of NSAID spontaneous adverse event reports: the Weber effect revisited. Drug Saf. 2001; 24:233–237. [PubMed: 11347725]
36. Moore N, Hall G, Sturkenboom M, Mann R, Lagnaoui R, Begaud B. Biases affecting the proportional reporting ratio (PPR) in spontaneous reports pharmacovigilance databases: the example of sertindole. Pharmacoepidemiol Drug Saf. 2003; 12:271–281. [PubMed: 12812006]
37. Center for Substance Abuse Treatment. Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction. Rockville (MD): Substance Abuse and Mental Health Services Administration (US); 2004.

Table 1

Summary of Adverse Event Cases, Methadone and Buprenorphine

Case characteristics	Buprenorphine n=7283	Methadone n=14915
Age, years†	38.5±20.2	38.4 ± 16.3
Gender‡		
Male	3192 (43.8%)	5009 (33.6%)
Female	2672 (36.7%)	4271 (28.6%)
Unspecified	1348 (18.5%)	5701 (38.2%)
Drug as primary/secondary suspect	5890 (80.9%)	9231 (61.9%)
Adverse Reaction		
Ventricular Arrhythmia	132 (1.8%)	1729 (11.6%)
QTc prolongation/torsade de pointes	19 (0.3%)	390 (2.6%)
Torsade de pointes	10 (0.1%)	252 (1.7%)

Values reported as N (%) and mean±standard deviation unless noted

† Age not available for 2046 (28.1%) buprenorphine and 3197 (21.4%) methadone cases

Table 2

Suspected Role of Methadone vs. Buprenorphine Reported in Cardiac Arrhythmia Events

Ventricular arrhythmia and cardiac arrest		
	Buprenorphine	Methadone
Drug role	n=132	n=1729
Primary or secondary	84 (63.6%)	1570 (90.8%)
Interacting	2 (1.5%)	18 (1.0%)
Concomitant	46 (34.8%)	141 (8.2%)

QTc prolongation/Torsade de pointes		
	Buprenorphine	Methadone
Drug role	n=19	n=390
Primary or secondary	5 (26.3%)	319 (81.8%)
Interacting	0 (0.0%)	22 (5.6%)
Concomitant	14 (73.7%)	49 (12.6%)

Torsade de pointes		
	Buprenorphine	Methadone
Drug role	n=10	n=252
Primary or secondary	0 (0%)	214 (84.9%)
Interacting	0 (0%)	16 (6.3%)
Concomitant	10 (100%)	22 (8.7%)

Table 3

Characteristics of Buprenorphine-Associated Torsade de Pointes Cases

Verbatim drug name	Sex	Suspected role	Death	Other QT-prolonging drugs
Buprenorphine	F	Concomitant	No	Methadone, itraconazole
Buprenorphine	M	Concomitant	No	Methadone, ciprofloxacin
Buprenorphine HCL	M	Concomitant	No	Methadone, ciprofloxacin
Subutex	M	Concomitant	No	Amiodarone
Subutex	M	Concomitant	No	Amiodarone
Buprenorphine hydrochloride	M	Concomitant	No	Amiodarone
Buprenorphine/naloxone	F	Concomitant	No	Methadone, voriconazole
Buprenorphine	F	Concomitant	No	Fluoxetine, alcohol
Buprenex	F	Concomitant	Yes	Fluoxetine
Buprenex	F	Concomitant	Yes	Cyclobenzaprine

Table 4

Proportional Reporting Ratios of Cardiac Arrhythmia Events for Buprenorphine, Methadone, and the Combination (1969-June 2011)

	Ventricular arrhythmia and cardiac arrest					
	Drug		All other drugs			
Drug	Event	No event	Event	No event	PRR (95% CI)	χ^2
Buprenorphine	132	7151	79020	4731912	1.10 (0.93–1.31)	1.2
Methadone	1729	13186	77423	4725877	7.20 (6.88–7.52)	8027
Methadone+buprenorphine	7	117	79145	4738946	3.44 (1.67–7.06)	12.3
	QTC prolongation/Torsade de pointes					
	Drug		All other drugs			
Drug	Event	No event	Event	No event	PRR (95% CI)	χ^2
Buprenorphine	19	7264	12148	4798784	1.03 (0.66–1.62)	0.01
Methadone	390	14525	11777	4791523	10.7 (9.66–11.8)	1538
Methadone+buprenorphine	5	119	12162	4805929	16.0 (6.8–37.7)	70
	Torsade de pointes					
	Drug		All other drugs			
Drug	Event	No event	Event	No event	PRR (95% CI)	χ^2
Buprenorphine	10	7273	4028	4806904	1.64 (0.88–3.05)	0.9
Methadone	252	14663	3786	4799514	21.4 (18.9–24.3)	1011
Methadone+buprenorphine	4	120	4034	4814057	38.5 (14.7–101.1)	142

PRR = proportional reporting ratio