Data Source & Extraction

Drug manufacturers marketing products in the United States are required by law to report adverse events that they become aware of to the FDA. Anyone can report to the FDA, including clinicians, patients, caregivers, etc. FDA de-identifies these data and makes them available to the public in structured quarterly release files, but case narratives which contain details of the case are not included as part of this public release, but identity redacted versions can be obtained by request. Quarterly public release files from the FDA Adverse Event Reporting System (FAERS) were used to identify potential case reports of interest, for the time period October 1, 2010 through March 31, 2016. Case note extraction was conducted by FDA on November 29, 2016 and included initial and follow-up notes. Relevant data available in these files included: FAERS record number, dates of event, receipt by sponsor, and FDA transmission date, substance involved, outcomes, and sponsor’s causality assessment.

Public FAERS data are coded using MedDRA preferred terms (multiple versions over time), assigned by the manufacturer or FDA depending on which organization received the report initially. MedDRA® the Medical Dictionary for Regulatory Activities terminology is the international medical terminology developed under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). MedDRA® trademark is owned by IFPMA on behalf of ICH.

Screening Criteria

For the outcome, because fatal overdose deaths have the potential to have been misclassified, a broader set of records were identified and then screened, followed later by manual causality assessment. First, all deaths involving Vivitrol were requested, based on outcome code (“DE” for death) or the search expression death among preferred terms. Second, possible overdoses were identified using exact matches with natural language processing (NLP). All reported preferred terms fields were reviewed to identify possible terms related to opioid overdose, including common signs, symptoms, and secondary complications.

The resulting list of search terms comprised: overdose, overdoseage, completed suicide, intentional overdose, accidental overdose, cardiac arrest, coma, loss of consciousness, cardiac disorder, heart rate decreased, immobile, sedation, sluggishness, toxicity to various agents, circulatory collapse, cardiac death, cardiac failure, cardiogenic shock, death neonatal, exposure to toxic agent, hemiplegia, stroke, oxygen saturation decreased, pulmonary oedema, respiratory failure, respiratory arrest, seizure like phenomena, transient ischaemic attack, hypoxic-ischaemic encephalopathy, pulmonary congestion, pulmonary embolism, acute respiratory distress syndrome, respiratory depression, respiratory arrest, unresponsive to stimuli.

Multiple Reports

FDA applies a processing logic to identify multiple copies of the same event using the isr field and follow-up flags, or in later versions the primaryid field. A second de-duplication process was applied to identify possible multiple events not identified by FDA, using exact matches for the four regulatorily reportable events: event date, age, sex, and reporter country. In addition, due to considerable missing data in structured fields, manual review was also conducted to de-duplicate cases.

Manual Abstraction & Causality Assessment

FOIA results consisted of portable document format (PDF) files with case narratives and transmission metadata. Identifying information, some details of event dates, and other elements were redacted by FDA. Narratives were manually reviewed by the study team to extract relevant information for all received cases using a structured instrument which included: date of first dose, time since
last dose of Vivitrol, indication (alcohol dependence, opioid dependence, unspecified), and other fields required for completeness scoring and causality assessment. In pharmacovigilance, causality assessment is the process of assessing the relationship between drug exposure and outcome (see Bhangale et al. [2] for a thorough description). Causality assessment was conducted using the case narrative notes, taking into consideration the Sponsor's causality assessment, but arriving at independent conclusions. The causality assessment was conducted initially by RS, and reviewed by ND, with differences of opinion discussed and adjudicated until there was concordance.

Completeness Scoring
In order to compare documentation of Vivitrol adverse events cases against an international standard and to assess if there was enough information to allow for a more complete analysis, we computed VigiGrade completeness scores, developed by the Uppsala Monitoring Centre of the World Health Organization (WHO-UMC) [1]. Dimensions accounted for in the VigiGrade score include time-to-onset, indication, outcome, sex, age, dose, country, primary reporter's occupation, report type, and the presence of informative free-text information. For outcome scoring in VigiGrade, death cases were penalized if cause of death was unknown. Possible scores range from 0.07 to 1.0, with each report starting at 1.0 and then subsequently penalized for each dimension lacking or containing limited information. Well-documented reports were those with VigiGrade of 0.80 or higher. Since only one dosage form of Vivitrol (380 mg) was marketed during the study period, no penalty was assessed for the lack of dose information, resulting in an actual range of possible scores from 0.079 to 1.0.

Outcome Definition
The overdose outcome was identified by combined review of narrative text and assigned MedDRA preferred terms. A fatal opioid overdose was defined as any death having mention of an overdose occurring after administration of Vivitrol, unless only non-opioid substances were specified (e.g., alcohol, benzodiazepines, anti-depressants, etc.). Fatal opioid overdose cases were limited to those for which the indication for Vivitrol was drug dependence, both alcohol and drug dependence, or indication unknown. In instances of discrepancy between de-identified FAERS data and the case record narrative, the latter was given higher priority because the Sponsor’s follow-up calls documented in the narrative details established that the patient was still living despite initial coding of “DE” in FAERS, for example, a case in which the spouse incorrectly reported their partner as dead, but was found to be living upon follow-up. In AE reports where the Sponsor’s narrative makes vitality status unclear, the cases were excluded by assuming them to be non-fatal. Deaths that were determined to be suicides were not included as overdoses, even if they involved the decedent ingesting a fatal amount of opioids.

If only the month and year was provided, the date for the event was set to the 15th day of the month. If date of death was redacted in the narrative, and the outcome of the AE was death, the event date was presumed to be the death date. If only the calendar year of overdose death was provided, time-to-event was considered missing.

Citations