

## **Limitations in Determining Spontaneous Adverse Event Reporting Rates and Comparing Atomoxetine to other ADHD Medications**

Adverse events (AEs) may be reported to a drug manufacturer by healthcare professionals (HCPs), consumers, regulators, attorneys, through scientific literature, and manufacturers' sales representatives. For individuals external to the manufacturer and regulators, reporting is voluntary, which leads to substantial underreporting. The magnitude of underreporting is not known and is likely to be variable across different products and manufacturers based on multiple factors, including the marketing status and history of the product, the familiarity of prescribers to the product's safety profile, utilization patterns, and manufacturers' AE ascertainment practices. The nature of this variability is such that newer products tend to have higher levels of reporting than products that have been on the market for many years. That is, it is likely that a greater proportion of the AEs that occur in the population of patients taking a newer drug are reported to the manufacturer than for an older drug.

A product that is under an active marketing campaign will have sales representatives detailing potential prescribers on the product. During these interactions the sales representatives may learn about AEs with the product, which they are required to report. Sales representatives are much less likely to be detailing prescribers on a product that has been on the market for decades and has generic competition. In the example of atomoxetine and methylphenidates, sales representatives are discussing atomoxetine with prescribers every day, thus increasing the likelihood that they will learn of an AE that will be reported to Lilly and subsequently to FDA. In recent years, there have been far fewer sales representatives detailing prescribers on methylphenidates and thus this path of AE reports has been more limited for methylphenidates.

Differences in approved indications and patient populations across products may also influence the effect of sales representatives' capture of AE reports. For example, since atomoxetine was the only ADHD medication approved for use in adults for the first period of its marketing availability, only atomoxetine sales representatives were detailing prescribers for adults, therefore increasing the likelihood that adult AEs would be reported through sales representatives. Other ADHD medications were only used in adults through off-label prescribing. Since sales representatives may not detail prescribers for off-label indications, this route for the ascertainment of adult AEs was limited for other ADHD medications prior to the approvals of the adult indication.

Recent advances in technology and AE systems have also influenced the capture of AE reports. When some of the older ADHD medications were new to the market, programs and systems designed to enhance reporting of AEs such as toll-free call centers, the electronic submission of reports, and the MedWatch program were not in existence or less widely used. Therefore, at the time these drugs were new and concern over their safety profiles was likely to be greatest, the pathways for ascertainment of AE reports were not as efficient as they have become in recent years.

Prescribers' familiarity with a product's safety profile can also influence the level of AE reporting. Before a prescriber becomes familiar with a product, s/he may be more likely to contact the manufacturer or sales representative with questions about the product. During these interactions, the prescriber may mention AEs, which are then entered into the manufacturer's database and reported to FDA. As experience with a product grows, both collectively and for the individual prescriber, expected AEs may be less likely to be reported.

In addition to the biases of variable reporting, the comparison of reporting rates across different products cannot be adjusted for the differences in baseline risks of the patient population of each product. Multiple factors are considered in the clinician's decision on which drug to prescribe. If baseline risk of a particular AE influences this decision, that can have an impact on reporting rates, independently of possible causality. This is known as channeling bias because patients with a particular pre-existing risk profile are "channeled" into use of a particular drug. The effects of channeling bias are difficult to ascertain with spontaneous AE reports, but may be substantial.

Many of the limitations discussed above as well as others are cited in the FDA Guidance for Industry on Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (2005), which recommends that comparing reporting rates calculated from spontaneous AE reports be viewed with extreme caution and considered exploratory or hypothesis-generating. In addition, the guidance outlines the following considerations regarding reporting rates:

- Calculation of the incidence rates of AEs in the product-exposed population is the hallmark of pharmacoepidemiologic risk assessment. Spontaneous data do not allow for incidence rate calculation due to difficulties in identifying all cases of the event (underreporting in the numerator) and in estimating the size of the exposed population (denominator).
- Limitations associated with estimation of patient exposure include difficulty of obtaining duration of exposure; inability to exclude patients not at risk, for example patients whose exposure was too brief or who had too low a dose; and inability to stratify patient exposure by indication for use.
- Despite these limitations, FDA recommends calculation of crude AE reporting rates using total number of reported cases in the U.S. in the numerator and estimates of national patient exposure to product in the denominator. Whenever possible, number of patients or person-time exposed should be the estimated denominator rather than numbers of prescriptions or kilograms of product sold.
- Comparisons of reporting rates and their temporal trends can be valuable, but should be viewed with extreme caution because of the inherent uncertainties in the numerator and denominator used. Reporting rates should not be considered incidence rates for absolute or comparative purposes. Comparison of reporting rates should be considered exploratory or hypothesis-generating.

- Comparison of reporting rates with background rates (population incidence rates) can be valuable, but must be interpreted with consideration of the associated limitations. Ideally, the background rate for comparison is in a subpopulation similar to the exposed population (e.g., premenopausal women, diabetics), however, estimates in these populations are often not available. Additionally, there are often differences between reporting rates and background rate estimates with respect to data sources, diagnostic criteria, and duration of time at risk.
- The extent of underreporting of spontaneous events is not known, but is assumed to be substantial. Therefore, in comparison to a background rate, a reporting rate that is greater may be a strong indicator that the true incidence rate of the AE with the drug is sufficiently high to be of concern. However, in this situation, the factors that may influence spontaneous reporting must be considered, including publicity, length of time the product has been on the market, severity of the event, etc. Also because of underreporting, a reporting rate that is lower than the background rate does not necessarily show that the product is not associated with increased risk of a particular AE.

In conclusion, any interpretation of the reporting rates for atomoxetine and other ADHD medications must be made with the consideration of the substantial biases inherent in spontaneous AE reporting, including biases associated with the marketing status and history of each product, utilization patterns, AE reporting systems, possible channeling bias, and others. While an elevated reporting rate may suggest the need for additional investigation, a reporting rate alone should not be the basis of decision-making.