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Monitoring the Safety of Medicines

Used Off-label

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The views expressed are those of the author, and not necessarily those of the US Food and Drug Administration.

The label of a medicine contains important information on the conditions of use for that medicine. These conditions of use typically include the indication, the dosage, the frequency of administration, and the route of administration. Other important conditions of use can include the age range of patients, the duration of treatment, and contraindications to usage of the medicine. Deviations from the conditions of use set forth in the label constitute off-label use.

In the US, off-label use is legal. While FDA regulates the marketing of medicines, it does not regulate prescribing practices.

Off-label use is also common. One study (Radley et al. Arch Intern Med 2006; 166:1021-1026) documented that approximately 21 per cent of drug use mentions in office-based practice were for off-label uses. Off-label use may occur for a variety of reasons. For example, in the case of diseases for which no adequate, labeled treatment exists, off-label use may be common. Additionally, because for many years the use of medicines in children was not studied, there has been extensive off-label use in children. (There are ongoing efforts to correct this situation.) While some instances of off-label use may be supported by scientific publications, the study above by Radley and colleagues found that 73% of off-label use had little or no scientific support. In some cases, off-label use may become part of accepted practice, and may be part of professional society guidelines.

Because off-label use is common, there is an important public health need to monitor the safety of medicines when used off-label. Monitoring the safety of medicines in off-label settings is necessary to inform the usage of medicines in these settings. While it would be ideal to have formal study of medication safety

in these settings, such studies are often not available. Thus, safety monitoring plays a critical role. Data derived from monitoring safety in the off-label setting can also potentially refine our understanding of the safety of the medicine when used according to the label. In addition, data derived in the off-label setting may serve as a stimulus for more formal study.

There are many specific concerns that need to be addressed when monitoring the safety of medicines in the off-label setting. For example, many factors that could affect the safety of the medicine could be different in the off-label setting compared to the on-label setting. These factors include the age of patients, the range of co-morbidities, the use of concomitant medications, drug-disease interactions, and differences in pharmacokinetics and pharmacodynamics.

Despite the importance of monitoring the safety of medicines in the off-label setting, there are many challenges that this situation presents for a pharmacovigilance system. First, the many well known general limitations of a spontaneous reporting system apply to the identification and analysis of spontaneous reports in the off-label setting. Second, spontaneous reports do not always contain the indication for usage or other details that would allow one to determine that the medicine was used in a manner not consistent with the product's label. Third, the identification of an adverse drug reaction in the off-label does not necessarily mean that this reaction is limited to the off-label setting. Despite these limitations, spontaneous reports can be useful in determining adverse drug reactions when medicines are used off-label.

To supplement data from spontaneous reports, drug utilization databases may be helpful in monitoring off-label use of medicines. Though such databases do not typically contain information on indication for usage, they can be helpful in identifying other aspects of off-label use. For example, drug utilization data may shed light on the age range of patients using a medicine, the duration of therapy, concomitant medications used, and the dosages prescribed. Review of such data may indicate that there is substantial off-label use, and thus may inform safety monitoring. Because drug use databases typically do not have any information on medical diagnoses, they are not suitable for identifying adverse events. Nonetheless, they can be useful for identifying trends in drug usage that may require further study in other databases. Administrative healthcare databases that contain information both on drug use data and medical diagnoses can also be useful for identifying trends in off-label use, though medical record review may be necessary to determine the indication for usage. Electronic medical records may be more useful than administrative healthcare databases, if indication for usage is linked to the drug prescribed. Finally, published clinical trials studying off-label uses may be a useful source of information on adverse drug reactions. However, the limitations of clinical trials for ascertaining adverse event information, especially rare adverse events, are well known.

In summary, the off-label use of medicines is common. Monitoring of adverse events in this setting is important, though there are many challenges in doing so.