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Risk Evaluation and Communication

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All medications have risks. Although many different definitions exist, risk is usually defined as a potential harmful outcome that can occur with a known or unknown probability [1]. Some medication-related risks are more serious than others and some are well understood whereas others are clouded by uncertainty. The responsibility of ensuring that medications are used as safely as possible is shared by the pharmaceutical companies that develop, investigate, manufacture, and market medications; the governmental agencies charged with regulating these processes; the healthcare providers who prescribe or dispense prescription medications and make recommendations concerning the use of over-the-counter products; the governmental agencies that license and regulate healthcare providers and healthcare facilities; and the patients who ultimately must decide whether or not to use a medication and, in most cases, have control over how they use the medication.

Since passage of the Kefauver–Harris Amendments to the Food, Drug, and Cosmetic Act in 1962, market approval of a new drug in the United States has required that the Food and Drug Administration (FDA) determine that the medication is safe and effective (see Chapter 1) [2]. Similar criteria are used by regulatory agencies in other countries as well [3]. For example, in Europe, the European Medicines Agency (EMA) is responsible for the scientific evaluation of medicines for the 28 member states of the European Union. Similar to the FDA, the EMA is required to evaluate whether medications are acceptably safe and effective prior to drugs being permitted a marketing authorization or product license [4]. Other chapters in this book provide information concerning how these determinations are made (see Chapters 1 and 8). Here, we simply reiterate that even medications that are judged as meeting safety standards have risks.

A drug is considered "safe" if the risks associated with it are deemed to be acceptable [5]. In some cases, medications with substantial and serious risks are judged as meeting safety standards because the benefits of the medication outweigh the risks. This is most often the case for medications used to treat debilitating or life-threatening illnesses where few other effective treatment options are available. It is also important to recognize that the safety of a medication is not solely an inherent property of the medicine, but also the circumstances in which the medication is used (e.g., expertise of

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prescribers, procedures used to monitor potential adverse effects, presence of interacting medications). Thus, many medication risks may be minimized through the implementation of appropriate risk management strategies.

To minimize medication risks following market approval, all parties involved in the medication use process must have access to up-to-date information concerning potential risks, including measures that can be used to prevent or control these risks. Moreover, this information must be provided in a timely manner and in a way that is understood by the target audience and that facilitates informed decision making. In this chapter, we discuss some of the clinical and methodologic challenges that must be addressed to meet these goals. We also discuss approaches that are currently used to enhance the dissemination and usability of information concerning medication risks. We conclude by suggesting directions for future research in this area.

Clinical Problems to Be Addressed by Pharmacoepidemiologic Research

Five major clinical issues involving medication risk communication need to be addressed by pharmacoepidemiologic research.

First, one must determine the information that patients need about medication risks to be able to participate in shared decision making and use medications safely. Most medications have many risks (e.g., stomach upset, liver toxicity, cancer, potential for allergic reactions) and each risk has many dimensions that can affect judgments of acceptability. These dimensions include probability, severity, controllability, reversibility, and time of onset (e.g., whether potential harm usually occurs soon after initiation of therapy or may not arise for many years) [6,7]. In addition, although uncertainty is an inherent characteristic of any risk, the risks associated with some medications are more uncertain than others. For example, the risks associated with medications that have been used for many years in a large number of patients may be fairly well understood [8]. Conversely, we often have limited understanding of the risks associated with recently marketed medications, particularly those that are first-in-class, and previously unrecognized risks may continue to emerge for several years after a medication is first marketed. Given that it is probably neither feasible nor desirable to provide comprehensive patient education concerning all medication risks, there is a need to determine how different types of information should be prioritized.

Second, one must determine what information patients need about potential medication *benefits* to be able to make informed decisions regarding the need for therapy and the selection of a specific treatment when therapeutic alternatives are available. Serious risks associated with a particular medication may be acceptable if the medication offers substantial benefits, especially if no acceptable therapeutic alternatives are available [7]. However, the same risk may be unacceptable for a less effective medication that does not provide unique advantages over other treatment options (see Chapter 35).

Third, there is a need to identify the most appropriate targets (e.g., healthcare providers, patients with a specific health problem or taking specific medications, consumers in general) for different types of communications and the most feasible and cost-effective way to communicate the information needed by different target audiences. Although patients can obtain information about medication risks and benefits from a wide variety of sources, most express a preference for obtaining this type of information from their healthcare provider [9,10]. Yet healthcare providers often struggle to remain abreast of recent research findings given the sheer volume

of emerging information as well as conflicting findings from different studies [11]. In addition, physicians may lack the skills in evidence-based medicine needed to critically evaluate the literature [12,13].

Fourth, one must determine how information should be tailored to individuals' needs, preferences, abilities (e.g., health literacy and numeracy), risk status (i.e., presence of factors that affect the probability/severity of medication side effects; presence of factors that affect benefits that might be gained by using the medication and risks associated with deciding to forego therapy), and current status in the medication use process (e.g., deciding whether to initiate therapy with a new medication; self-managing a stable, chronic medication regimen). Tailoring is also needed when working with special populations (e.g., children, individuals with cognitive impairments).

Finally, there is a need to address ethical issues that arise when communicating information about medication risks and benefits. Potentially, educating patients about medication risks and the uncertainty associated with experiencing medication benefits may increase patient reluctance to use an effective prescribed medication [14].

Methodologic Problems to Be Addressed by Pharmacoepidemiologic Research

In addition to the clinical issues described above, five major methodologic issues need to be addressed by pharmacoepidemiologic research. First, effective risk communication requires the availability of high-quality information concerning the risks and benefits of different therapeutic options, including the option of foregoing treatment. This need goes beyond simply knowing that a certain risk/benefit is possible. Information is needed concerning all the risk dimensions discussed in the previous section (e.g., probability, severity, controllability, reversibility, time of onset). Moreover, the information included in risk communications must be relevant to the target audience. Thus, the generalizability (and limits to generalizability) of pharmacoepidemiologic studies must be well understood.

Second, there is a need to determine the best format for providing risk/benefit information. Most risk communications include probabilistic information, which even healthcare providers can find difficult to interpret [15–17]. A wide variety of formats can be used to convey probabilistic information: qualitative descriptors (e.g., common, rare), numbers (e.g., absolute risk, relative risk, odds ratios), and graphics (e.g., bar charts, pictographs). Many studies have demonstrated that the format used to express probabilistic information can have a substantial impact on judgment and decision making [18,19]. Experts recommend against providing risk information only in relative terms, isolated from baseline rates and other information that would contextualize the risk [20,21]. Experts also recommend that verbal descriptors should either be avoided or defined explicitly in numerical terms as part of the risk communication [22,23]. However, many questions remain concerning the optimal way to convey this type of information.

Third, there is a need to better understand the factors that influence individual differences in how people perceive and respond to risk. Risk evaluation is not simply a cognitive exercise where estimates of probability and severity are entered into a mathematical formula to derive an estimate of acceptability that is invariant across individuals. People respond affectively to risk information [24–27] and different people may respond differently to the same information based on their past experiences and tolerance of uncertainty.

Fourth, there is a need to develop communication strategies that address the tendency for

patients and providers to overestimate the probability and magnitude of medication benefits. Hoffman and Del Mar identified a "medical optimism" among patients who express overly optimistic expectations about interventions, while simultaneously underestimating the chance of harm associated with treatments [28]. In comparison, it might be expected that clinicians have more accurate expectations of the benefits and risks associated with treatments. However, it has been demonstrated that, similarly to patients, clinicians rarely hold accurate expectations of treatment benefits and harms and also tend to overestimate benefit and underestimate risk [29]. Potential reasons for this may include a tendency to make decisions based on an understanding of how a treatment works as opposed to how effective it is [30] or may result from deficits in training. Hoffman and Del Mar also propose the existence of therapeutic illusion, "an unjustified enthusiasm for treatment on the part of both doctors and patients," as a factor that may influence perceptions [29]. Clinicians' understanding of risk and benefits is essential to ensure that patients receive accurate information to make unbiased and informed decisions about their treatments, so this is clearly an issue that requires resolution.

Fifth, there is a need to determine the most appropriate methods to use when evaluating communication effectiveness. In most cases, the ultimate objective of risk communications is to improve health outcomes by reducing the incidence of adverse events. However, it is helpful to consider the causal mechanisms through which desired effects on health outcomes might be achieved. As shown in Figure 39.1, the most proximal effects of risk communications are likely to be increased knowledge and, in many cases, emotional arousal. Next, the information communicated may be incorporated into decision-making processes. At this point, it is important to consider whether the purpose of the risk communication is to inform or persuade. If the purpose of the communication is purely informational, it would not be appropriate to evaluate message effectiveness in terms of the specific decision made. However, many risk communications include components that advocate specific actions (e.g., initiating precautionary behaviors to reduce a specific risk) and, therefore, have a persuasive intent. In these cases, the message would probably not be considered effective unless the desired behavior changes were realized. Evaluators must also give careful consideration to the time required for different types of effects to become evident [31]. For example, one would expect knowledge change to be evident immediately following message exposure. However, effects on health outcomes may require substantial time to become evident.

Two additional issues related to the evaluation of communication effectiveness deserve special attention. First, when evaluating the effect of risk communications on knowledge, investigators must determine what knowledge is needed for patients to make informed decisions and use medications safely. For example, is it important for patients to know that the probability of experiencing a particular medication side effect is 1%? Or is it sufficient to know that the side effect is possible, but unlikely? Reyna has argued that informed decision making does not require recall of precise verbatim information (e.g., exact probabilities), but does require understanding and recall of the essence of the information communicated [32,33]. Second, when evaluating communication effectiveness, it is important to consider unintended as well as intended effects. Risk communications concerning one medication have the potential to raise concern about unrelated medications and result in patients discontinuing efficacious medications that pose minimal risks. Unintended consequences might best be evaluated by assessing changes in health-related quality of life and changes in the use of medications other than those that are targeted by the risk communication.

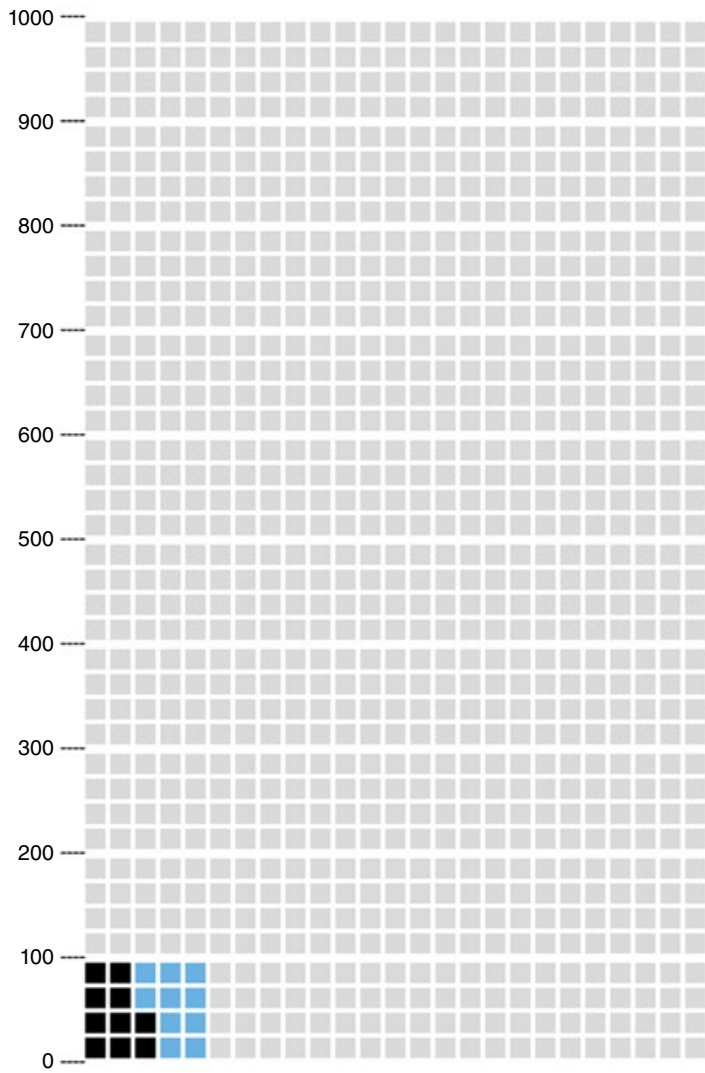

Figure 39.1 Sample pictograph.

Currently Available Solutions

Health Professional and Consumer Medication Information

Many countries have implemented regulatory measures in response to the challenges of communication about medication risks and benefits. For example, in order to promote the principles of transparency and develop methods of improving risk communication, the EMA requires the production of several documents which all play a role in risk/benefit communication. These include the European Public Assessment Report (EPAR), the Risk Management Plan (RMP), and the Patient Information Leaflet (PIL).

The EPAR is a lengthy public document which details the scientific assessment of a pharmaceutical product. These regulatory documents

are written for professionals, but pharmaceutical companies must also provide a user-friendly lay summary. The aim of the lay summary is to communicate how the decision to license the medicine was made. It is essential to ensure that such documents can be understood by potential users, and user testing is one potential method for ensuring that readability is optimized [34].

To adhere to good pharmacovigilance guidelines set out by the EMA, medicinal products are authorized "on the basis that in the specified indication(s), at the time of authorisation, the risk-benefit balance is judged to be positive for the target population" [35]. The EMA requires that pharmaceutical companies publish RMPs which must include information on the medicine's safety profile, how any risks will be prevented or minimized in patients, any plans for studies or other activities to gain more knowledge about the safety and efficacy of the medicine, and to assess the effectiveness of risk minimization measures. There is a requirement that RMPs are updated and modified as needed throughout the lifetime of the medicine, as additional information becomes available.

Patients in the UK and throughout the countries of the European Union must, by law, receive written information with their medicine which includes some communication on the risks and benefits associated with taking it. In 1992, a Directive from the European Commission on the labeling of medicinal products for human use mandated that all medicines are accompanied by a regulated patient information leaflet (package insert) inside the medicine box [36]. The Directive aimed to provide a standardized format for patients in order to provide consumer protection and ensure access to full and comprehensible information about medicines. For some patients, this might be the only written information they receive about their medicines.

European PILs follow a standardized format and include information about the following: potential side effects and their estimated frequency; what the medicine does and what it is for; dos and don'ts; and how to take the medicine [37]. Effective and balanced risk communication occurs when there is presentation of information about both the risk of harm and likelihood of benefit associated with taking a treatment. European PILs currently contain both textual and numerical descriptions of the estimated frequency of harms associated with taking the drug, as well as an indication of severity, aiming to inform patients about potential adverse effects in order to encourage help seeking, but also to support patients in making informed decisions about treatments.

Initially, guidance required European pharmaceutical license holders to present the risk of harm using a combination of qualitative and quantitative descriptions for five bands of risk frequency, ranging from "very common" (>10% frequency) to "very rare" (<0.01%). While the inclusion of the risk frequencies meets patients' identified need for information about the side effects of their treatments [38], the use of percentages to communicate numerical information about risk of harm can lead to overestimations of risk [39], which have been noted both in patients and in doctors [40]. Consequently, updated guidance recommends the use of frequency bands using a natural frequency numerical format (e.g., "less than 1 in 100"). UK PILs now communicate risk using the following regulatory standard [41].

- Very common – occurs more frequently than 1 in 10 administrations of a drug.
- Common – occurs in between 1 in 10 and 1 in 100 administrations of a drug.
- Uncommon – occurs in between 1 in 100 and 1 in 1000 administrations of a drug.
- Rare – occurs in between 1 in 1000 and 1 in 10 000 administrations of a drug.
- Very rare – occurs in less than 1 in 10 000 administrations of a drug.
- Frequency not known.

Use of the five verbal terms (very rare; rare; uncommon; common; very common) alone has

been shown in a number of studies to produce risk estimates that are inconsistent with the assigned frequencies of incidence. For example, "common" was assigned to incident rates between 1% and 10% but was found to result in mean risk estimates of 45.3% by members of the public asked about a hypothetical antibiotic [40]. Furthermore, the term "rare," which had been assigned to rates of 0.01% to 0.1%, produced average risk estimates of 8%. These findings were replicated in a study with a similar study design but which asked people using statin (cholesterol-lowering) medicines to respond to information about real side effects (and their incidences). The "common" side effect of constipation was estimated to occur in 34.2% statin users, while the "rare" side effect of pancreatitis was estimated to occur in 18% users [42]. If these significant overestimates of risk frequency were translated into behaviors (such as deciding not to take the medicine), then their use would be problematic.

One notable point from these and other studies of risk estimation is the high levels of variation in estimates found in study samples. In the study by Berry *et al.*, the standard deviations around the estimates of "common" and "rare" were 22.5% and 7.5%, respectively, a pattern replicated elsewhere [42]. Risk estimates among people are highly variable, which may in part result from relatively stable differences between them in their perceptions of risk susceptibility or their numeracy skills [43]. However, verbal terms appear to add another layer of variation and it seems to be much more difficult to achieve consensus in their meaning than it is for numerical risks descriptors.

Verbal terms do have some strengths, as they may be seen as less intimidating by some patients and as closer to the everyday language of risk; in conversation, people will tend to use words to give a gist or estimate of the degree of risk associated with an uncertain event. However, when used in the context of medicine side effects, words seem to have framing effects, tending to produce inflated estimates of risk that might lead patients to make inaccurate judgments [44]. PILs, as produced currently according to European law, are perceived as containing information about medicines as risky, side effect-inducing products [45]. Therefore, it is important that the terms used, both in writing and in conversation with patients, are proportionate and not prone to misinterpretation.

When space allows, using graphical representations of risk (e.g., bar charts, pictographs) can be helpful, although they are not a panacea and evaluation is essential. However they do seem to have positive effects on accuracy of risk estimates, as well as other benefits, and appear particularly useful for information users who are less skilled or adept at risk interpretation [46]. A sample pictograph is shown in Figure 39.1. In this graph, each square corresponds to one person in the at-risk population. The black squares depict the risk of experiencing liver toxicity within five years of initiation of therapy with Medication B. Thus, this figure suggests that 10 out of every 1000 patients taking Medication B will experience liver toxicity within five years of therapy initiation. The dark gray squares depict the increase in risk associated with Medication A. That is, out of every 1000 patients treated with Medication A, 10 extra cases of liver toxicity would be expected to develop among individuals taking Medication A as opposed to Medication B. Pictographs provide a relatively simple way to convey information concerning both relative and absolute risk. However, they may not be useful when the risk(s) of interest occur very infrequently (e.g., 1 case/10 000 patients treated).

One criticism that patients express about European regulated PILs is that, while information about side effects is valued, when included in written information it can provide an overly negative impression of the medicine. Consequently, in order to support patients to make balanced and informed decisions about treatments, there is a need to also provide information about the

likelihood of benefit from the treatment alongside the likelihood of harm. Currently, there is no consensus on the best format for the presentation of this type of positive information although the EMA notes that benefit information should be compatible with the Summary of Product Characteristics, a document required for the licensing of a drug, and should not be promotional.

The inclusion of information about the potential benefits of medicines in written medicines information is not without its challenges. As noted previously, there is a tendency for patients to overestimate the benefits of their treatments [28] and this can translate to "concern and upset" for patients when they are provided with numerical information that contextualizes the likelihood of benefit they receive from their treatments. A series of qualitative studies exploring patient perceptions and opinions on the provision of textual and numerical benefit information in patient information leaflets have all presented similar findings.

Hamrosi and colleagues recruited focus groups of medicine users in the UK and Australia and provided information about the medicine clopidogrel in two different formats, which had been revised specifically for the study [47]. The revised leaflets contained additional benefit information about clopidogrel in either a text-only format or a numerical format based on the number needed to treat (NNT) to prevent a heart attack or stroke. The NNT statement was written as follows, based on the best available clinical trial data:

> "If 100 people took this medicine for 2 years:
> - 3 of them would be saved from having a heart attack
> - 1 of them would be saved from having a stroke"

A key finding from this study was that while the inclusion of benefit information was valued and seen as a positive addition to the leaflet, the numerical benefit information provoked strong feelings of shock and surprise at the perceived low chance of benefiting from treatment. Some participants did not understand the numerical information, while others struggled to comprehend the magnitude and made an assessment of potential benefit based on a crude interpretation of the data.

Similar research has been undertaken exploring patient opinion and perception of different presentations of benefit information for medicines with different magnitudes of risk. In a focus group, study participants were presented with benefit statements for two different drugs (i.e., sumatriptan and simvastatin) using one of three different numerical formats (percentages, natural frequencies, and NNT) [48]. An example of the different magnitude of benefit seen in the two drugs is presented as follows using the NNT format.

- If 4 people like you take sumatriptan, 1 of them will have a less severe migraine headache after 2 hours.
- If 20 people like you take simvastatin over the next 5 years, 1 of them will be stopped from having a heart attack or stroke.

Participants reported similar levels of shock and surprise at the perceived poor benefits from the two medicines. Other key findings included the following:

- Textual format information was preferred, but did not provide enough information to help contextualize the magnitude of benefit.
- The NNT format was frequently misunderstood.
- The natural frequency format was challenging to understand but when participants invested time to understand, they reported that it helped understanding.
- Numerical information was perceived as worrying, but it was valued.
- Some participants thought that if information on the chance of benefit is available, it should

> not be withheld from patients, who may want it to help with their decisionmaking.

One concern noted was that numerical benefit information has the potential to influence patient behavior and could lead to the rejection of a beneficial treatment, perhaps based upon the affect heuristic, a mental shortcut that results in decisions being made based on an emotional response to information rather than reason [49].

There is evidence that "patients" shown numerical benefit information are more likely to choose not to take a treatment, rather than when they are shown nonnumerical information [50]. The inclusion of numerical information on the chance of benefit can influence decision making resulting in a tendency to reject a treatment. This study also explored the impact of the provision of numerical information about side effects and found the opposite – when individuals are provided with nonnumerical side effect information, they are less likely to take a medication than those provided with numerical information about the likelihood of harm. A key finding from this study is that presenting side effect and benefit information in nonnumeric format appears to influence decision making in opposite directions. Although numeric information for both benefits and side effects may enhance decision making, providing numeric benefit information may decrease individuals' willingness to take the medicine, creating both an ethical dilemma for prescribers and providers and a public health concern for policy makers when the chance of benefit from a medicine makes its use attractive at a population level, but which may not be persuasive for individual patients.

In the United States, all prescription medications are required to have an FDA-approved package insert, targeted primarily for prescribers, that comprises the official product label. However, with a limited number of exceptions, there are no regulations that require patients to receive written information about medication risks/benefits when they obtain prescription medications. This is despite FDA recognition that:

> … people are able to make better decisions about their healthcare and better use of the prescription medications available to them when they are well informed about the medications they take. Access to useful written information about prescription medications is important to ensuring appropriate use of these products [51].

Since the late 1960s, the FDA has required that patients receive a patient package insert when they obtain prescriptions for oral contraceptives and estrogens [51]. In 1979, the FDA proposed regulations requiring that manufacturers develop and distribute written patient information, to be approved by the FDA, for all prescription medications. However, the regulations were revoked prior to implementation, based in part on assertions made by pharmaceutical manufacturers and other private sector stakeholders that the goals of the regulations could be accomplished without governmental regulation. Unfortunately, although the availability of consumer medication information has increased over the past 40 years, the quality of the materials distributed is variable and often poor [52]. For example, a study reported in 2007 found that although most pharmacies in the US distribute written materials with prescription medications, many of the materials failed to include information such as contraindications and precautions needed for safe medication use [53]. Notably, there was considerable variability in the consumer medication information distributed by pharmacies in the three countries examined: the US, Australia, and the UK. The materials distributed in the US were evaluated the least favorably.

In an attempt to assist private sector developers, the FDA issued a Guidance document in 2006 entitled "Guidance on Useful Written Consumer Medication Information (CMI)" [51].

Table 39.1 FDA Action Plan criteria for defining useful consumer medication information.

Criterion
Drug names, indications for use, and how to monitor for improvement
Contraindications and what to do if they apply
Specific directions about how to use and store the medicine, and overdose information
Specific precautions and warnings about the medicine
Symptoms of serious or frequent possible adverse reactions and what to do
Certain general information, including encouraging patients to communicate with healthcare professionals, and disclaimer statements
Information that is scientifically accurate, unbiased in tone and content, and up to date
Information in an understandable and legible format that is readily comprehensible to consumers

Source: FDA [55].

Although this document does not establish regulations or legal requirements, it does provide recommendations for the content and format of CMI. As shown in Table 39.1, the Guidance document identifies eight criteria that can be used to assess the usefulness of CMI. It recommends that CMI not include all possible side effects but rather focus on those that are the most serious and most common. The Guidance document does not include any recommendations concerning how to communicate information concerning the likelihood of experiencing the side effects included. However, the examples provided in the Guidance suggest that no numerical information is needed. For example, in a section labeled "Possible side effects," the sample CMIs included in the Guidance state: "The most common side effects are mild upset stomach, diarrhea, and rash. Call your health care provider if these side effects bother you or do not go away" [51]. Finally, although the Guidance document highlights the need to write CMI using plain language principles, it does not recommend user testing to assess consumer comprehension.

A study conducted in 2008 assessed the extent to which CMI distributed by retail pharmacies in the United States met these criteria [54]. This study found that although 94% of the pharmacies visited by secret shoppers provided CMI with prescriptions for lisinopril and metformin, the materials met only about 60% of the eight criteria specified in the FDA Guidance document. Moreover, less than 50% of the materials were judged as meeting the criteria for comprehensibility/legibility, leading the investigators to conclude that "Private sector initiatives to provide useful CMI have failed."

The FDA Amendments Act (FDAAA-PL 110-85) of 2007 gave the FDA authority to require that pharmaceutical manufacturers submit a Risk Evaluation and Mitigation Strategy (REMS) to the FDA when deemed necessary to ensure that the benefits of a drug or biologic product outweigh its risks [55]. The FDA may require a manufacturer to submit a REMS as part of the initial drug approval process or in response to a new safety concern identified via sources such as adverse event monitoring systems, peer-reviewed biomedical literature, clinical trials, and the FDA's Sentinel Initiative [56]. As of February 2018, 73 products have an approved REMS.

All REMS must include at least one safety-related goal that identifies the specific health outcome that the REMS is designed to accomplish [55]. For example, the goal of the Prolia® (denosumab) REMS is to:

> … mitigate the risks of hypocalcemia, osteonecrosis of the jaw, atypical femoral frac-

tures, serious infections, and dermatologic reactions by:

1) informing healthcare providers and patients about the risks of (1) hypocalcemia, (2) osteonecrosis of the jaw, (3) atypical femoral fractures, (4) serious infections, and (5) dermatologic reactions associated with PROLIA®.
2) informing healthcare providers they should counsel patients about the risks associated with PROLIA® [57,58].

Risk Evaluation and Mitigation Strategies may include three major components [55]. First, the manufacturer may be required to develop a Medication Guide or a patient package insert which must be given to patients when a prescription is filled. Medication Guides must be approved by the FDA and become part of the official drug label. Approximately half of the currently approved REMS include a Medication Guide. However, the FDA can require a Medication Guide for drugs and biologic products that do not have a REMS if they determine that "certain information is necessary to prevent serious adverse effects, patient decision making should be informed by information about a known serious side effect with a product, or patient adherence to directions for the use of a product are essential to its effectiveness" [59]

Currently, approximately 600 products have Medication Guides. A 2012 study [60] examined all the Medication Guides that were available in April 2010 to determine the extent to which they met criteria of suitability for use among individuals with limited literacy skills [61]. Of the 185 Medication Guides assessed, only one was deemed suitable for individuals with low literacy skills. In a separate substudy, the investigators asked study participants to review three Medication Guides (taken one at a time) and their comprehension of the information contained in the Guides was assessed using "open book" methods. Participants answered an average of only 52.7% (SD 22.6) of the comprehension questions correctly, with lower scores observed among those with low and marginal literacy. Another study analyzed the results of 66 unique Medication Guide assessments submitted to the FDA between September 2008 and June 2012 [62]. On average, participants correctly answered 63.5% of questions concerning the primary drug risk(s). Only 20 Medication Guide assessments (30.3%) reported knowledge scores of 80% or higher. In general, higher knowledge scores were reported for Medication Guides that were part of a REMS that also included either a Communication Plan or Elements to Assure Safe Use, as described below. Other studies have also demonstrated that many patients have difficulty understanding the information contained in Medication Guides, including the critical safety information included in these documents [63,64]. Thus, although the number of Medication Guides available has expanded dramatically over the past decade, work to improve the usability of these Guides is urgently needed.

Second, a REMS may be required to include a Communication Plan targeted at healthcare providers [66]. For example, the Communication Plan for Prolia targets healthcare providers likely to prescribe this medication [67] and includes: (1) a letter to healthcare providers; (2) a letter to professional societies; (3) a patient counseling toolkit that includes a patient counseling chart for healthcare providers, a patient brochure, and a Medication Guide; (4) a journal information piece that was published quarterly for 12 months in three targeted journals; (5) a plan for the dissemination of REMS information at scientific meetings; and (6) a REMS Website that provides access to all the materials included in the REMS [68]. In line with FDA requirements, the landing page of the REMS website includes a statement encouraging patients and healthcare providers to report suspected adverse reactions and provides a link to the MedWatch reporting system (see Chapter 10), as well as toll-free telephone numbers to both the FDA and the manufacturer.

The final REMS component involves elements to assure safe use (ETASU). These elements

may include specific training, experience, or certifications for healthcare providers who prescribe or dispense the drug; restricting the types of healthcare settings in which the drug can be dispensed; special requirements for patient monitoring; documentation of required safety measures (e.g., laboratory testing); and patient enrollment in a drug registry.

Manufacturers are required to evaluate the effectiveness of their REMS 18 months, three years, and seven years after the REMS is approved. The results of these evaluations must be reported to the FDA so that it can determine whether modifications to the REMS are needed. Morris has provided guidelines for the assessment of REMS programs [69]. In 2011, the FDA created a REMS Integration Initiative to better understand the overall effectiveness of the REMS requirements and identify ways in which current regulations might be improved, particularly in ways that would reduce burdens associated with the regulations while not compromising the effectiveness of the program [70].

Patient–Provider Communication

Although healthcare providers have a professional obligation to counsel patients about medication risks, they may be reluctant to discuss potential risks with patients due to concern that it may decrease patient adherence to the prescribed medication regimen [71]. However, research suggests that the opposite is true. Patient–provider communication concerning potential medication risks and incorporation of patient preferences into the decision-making process may increase adherence and decrease the likelihood of premature discontinuation of therapy [72–74]. Unfortunately, research suggests that this type of communication during patient office visits is not the norm. For example, Sibley and colleagues found that medication concerns (e.g., expected side effects) were discussed in only 2.7% of visits involving diabetes patients and a nurse prescriber [75]. In another study, Richard and Lussier found that potential adverse reactions were discussed in fewer than 17% of physician office visits in which a new medication was prescribed [76].

In a study that analyzed audiotaped visits of patients with rheumatoid arthritis and their rheumatologist, Blalock and colleagues found that, when medication risks were discussed in relation to a medication that was being proposed for addition to the patients' regimen, the types of information most frequently provided were the importance of monitoring to detect potential problems early (30%), probability of side effect occurrence (29.8%), steps to take to minimize risk (25.5%), and severity (21.8%) [77]. When discussing risks associated with medications the patient was currently taking, only the importance of monitoring and steps to take to minimize risk were discussed in over 20% of the conversations. These findings highlight that patient information needs vary depending on their stage in the medication use process (e.g., deciding whether to initiate a new medication, managing a current medication regimen). This study also found that patients often were not able to extract meaningful gist from the information communicated by the rheumatologists [78]. For example, in 14% of the visits, patient coders indicated that it was not clear if the rheumatologist thought the medication was needed and, in 29% of the visits, the coders indicated that it was not clear if the rheumatologist was concerned about the safety of the medication. These findings highlight the need to focus not only on the types of risk/benefit information communicated, but also on the clarity of the communication.

Pharmacists also have a professional obligation to counsel patients about medication risks. Internationally, the rates of verbal counseling provided by pharmacists in community pharmacy settings tend to be low, but vary widely depending upon the research methods used. Observational studies using simulated

patients (i.e., actors trained to portray patients with a specific condition) tend to yield lower estimates of the rate of counseling [79]. Few states in the US require pharmacists to provide verbal counseling to patients when prescriptions are filled, with most states requiring only that pharmacists offer to counsel patients [80]. In a study using simulated patients, Svarstad and colleagues examined the rates of verbal counseling provided in 306 community pharmacies distributed across eight states in the US [81]. Risk communication, defined as providing information about at least one side effect or precaution, occurred in 17% of visits in which a prescription for amoxicillin was presented and 31% and 37% of visits in which a prescription for ibuprofen or paroxetine, respectively, was presented. Patients who filled a prescription in states with more strict regulations concerning pharmacist counseling (e.g., pharmacists required to provide face-to-face counseling) were more likely to receive risk information than patients in states with less strict regulations.

The Internet, Direct-to-Consumer Advertising, and Social Media

The availability of medication-related information via the internet, direct-to-consumer advertising, and social media has expanded dramatically since the turn of the century [82–86]. Unfortunately, the quality and accuracy of available information vary widely from source to source, and few safeguards are in place to allow consumers to evaluate the quality of information available from different sources [86,87]. Direct-to-consumer advertising (DTCA) and social media sites managed by pharmaceutical companies present special challenges. In a recent study that examined notices of violation and warning letters issued to companies by the FDA, 95% involved a branded drug website, online paid advertisement, or an online video [88]. Of the 179 violations examined, most involved the lack of risk information or the misrepresentation of benefit information. Although few countries allow DTCA, online materials travel across borders, presenting a global challenge [89].

Finally, some websites enable consumers to provide reviews of their medications, potentially opening up a Pandora's box for the spread of anecdotal information. A recent study examined over 100 000 reviews provided on the website WebMD [90]. The investigators found that in about two-thirds of the cases where differences in patient satisfaction ratings were observed for two drugs used to treat the same condition, the differences were consistent with findings reported in the published literature. However, where differences were observed, drugs with an FDA black box warning were reviewed less favorably by patients than would be expected based on the results of published studies, suggesting that these types of warnings may bias patient judgment and decision making. Clearly, more research is needed to better understand the effects of this type of internet-facilitated patient-to-patient communication.

The Future

Much of the literature on risk communication focuses on environmental risks and the risk of disease. The field of medication risk communication is still relatively young. The extent to which findings from other areas generalize to communication concerning medication risks remains unknown. Over the next few years, much will be learned as companies evaluate their REMS. For knowledge gain to be optimized, it will be important that REMS evaluation plans include a comprehensive assessment of both proximal and distal outcomes. The conceptual model depicted in Figure 39.2 may help to structure future evaluation efforts.

More basic research is also needed to assess how people process and use information about

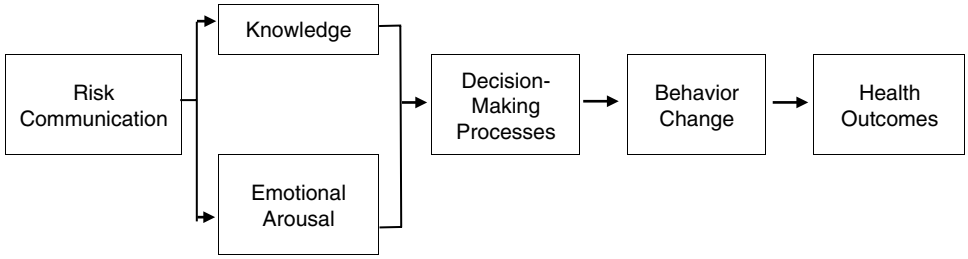

Figure 39.2 Conceptual model for evaluating the effectiveness of risk communication efforts.

medication risks. One promising approach involves the use of *fuzzy-trace theory* [91–94]. Briefly, fuzzy-trace theory posits that when an individual is exposed to risk information, two representations of the information are encoded in memory: a verbatim representation and a gist representation. The verbatim representation reflects the precise information received (e.g., 10% of patients who take Medication X experience Side Effect Y), whereas the gist representation captures the essential meaning of the information as understood by the receiver, in qualitative terms (e.g., Medication X can cause Side Effect Y). Different people exposed to the same information may form different gist representations, depending on their preexisting knowledge, previous experiences, emotional state, developmental stage, and worldview. A central tenet of fuzzy-trace theory is that when making judgments and decisions, people tend to rely on gist representations that are stored in memory and only retrieve verbatim representations when it is required by the task at hand. Further, this preference for gist processing of information increases with age and the acquisition of specialized expertise [94].

Currently, much of the risk communication literature focuses on how probabilistic information is best conveyed. From this perspective, the difficulty patients have in accurately recalling probabilistic information is viewed as problematic. However, from the perspective of fuzzy-trace theory, that conclusion might not be warranted. From a fuzzy-trace perspective, misunderstandings are most problematic when individuals interpret the gist of the information incorrectly. Numerical differences may have little effect on subsequent decisions. This possibility is supported by findings from an experimental study by Brewer *et al*. [95]. After reading a clinical vignette that portrayed a hypothetical patient, physicians in one group were asked whether the chance that the patient had a pulmonary embolism was greater or less than 1% and physicians in the other group were asked whether the chance that the patient had a pulmonary embolism was greater or less than 90%. Physicians in both groups were then asked to provide a point estimate of the chance of embolism and select from among a choice of treatment options. The irrelevant anchor (i.e., 1% versus 90%) used in the initial risk estimate had a large effect on physicians' subsequent point estimates of the probability of embolism, 23% versus 53% for physicians exposed to the low or high anchor, respectively. However, the treatment decisions made by the physicians were unaffected by the anchors. Thus, as suggested by fuzzy-trace theory, physicians appear to have based their treatment decisions on their gist representation of the information presented and were able to make rational decisions even in the presence of irrelevant information.

The findings described above illustrate the complexity of the risk communication process. Research using fuzzy-trace theory attempts to better understand the psychological processes

that underlie risk communication by systematically examining three central issues. Within the context of medication risk communication, these central issues are: (1) how do patients or clinicians extract gist from medication-related information obtained from a variety of sources (e.g., written information distributed by pharmacies when prescription medications are dispensed, direct-to-consumer advertising, healthcare providers, family/friends)? (2) what reasoning principles are invoked by contextual cues (e.g., format of the communication, images included in the communication) that affect patients' or clinicians' judgments and decisions concerning medication use? and (3) what factors (e.g., limited health literacy skills, emotional state) interfere with information processing and lead to errors in reasoning [92]? We believe that systematic research examining these types of issues has the potential to greatly expand current knowledge concerning communication of information regarding medication risks and benefits.

In conclusion, we began this chapter with the assertion that all medications have risks. The responsibility for communicating information about medication risks is shared by many entities within the healthcare system. In addition, we must recognize that we live in the Information Age. Information about medications and medication risks is disseminated by many outside the healthcare system, in some cases by individuals and groups without appropriate expertise and whose primary motive may not be the improvement of patient health outcomes. The challenge to investigators working in the field of pharmacoepidemiology is to develop communication strategies that reflect an understanding of both psychological and social issues that affect how message recipients interpret and use the information communicated.

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