

## IMPACT OF BENEFIT MESSAGES IN PATIENT PACKAGE INSERTS ON SUBJECTIVE DRUG PERCEPTION

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**Objective:** To explore the impact of the inclusion of a benefit message in a patient package insert on knowledge about medicines and on subjective benefit/risk perception. **Setting:** Female members of community social organizations, female relatives of psychology students, and caregivers to psychotic patients. **Nature of the study:** Randomized, controlled healthy human volunteer study with three parallel experiments, involving the inserts of *cisapride*, *itraconazol*, and *risperidon*. **Design:** Subjects were recruited in a convenience sample and randomized to one control and two intervention groups (one with a normal insert and one with an insert with a benefit message). **Material and methods:** Subjects were asked to read the inserts (using mock text in the control group) in 5 to 15 minutes. Knowledge of the medication was tested with 20 simple questions (to be answered Yes/No/Don't know) and benefit/risk perception with a five-point bipolar Likert scale. **Results:** In the three experiments respectively 89, 102, and 83 subjects were recruited. The provision of inserts increased the knowledge about medication in all the intervention groups. Thirty-one percent, 41%, and 54% of the subjects who read a normal insert agreed that the benefit of the medicine was greater than its risks, compared to 62%, 64%, and 70% of subjects who read an insert with a benefit message included ( $P < 0.05$  in all 3 experiments). **Discussion:** A hypothesis for further research is formulated: adding a section on benefit information within a patient package insert helps to integrate increased knowledge about medication into a more balanced benefit/risk perception.

**Key Words:** Drug labeling; Attitude toward health; Risk; Cognition; Pharmaceutical preparations

### INTRODUCTION

THERAPEUTIC SUCCESS IN modern medicine still relies heavily on the repeated self-administration of medicines by the patient. At the start of treatment, the patient

must be persuaded of the need to take the medicine, and at the same time, he/she must be informed about its risks. Moreover, the patient should be able to react appropriately when something harmful occurs, expected or not. The first step toward provision of such information began in 1992, when the European Union issued a Directive (1) imposing the insertion of a readable, full information leaflet (in most cases 400 to 600 words long) in each drug package (2,3). In the United

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States, successive similar attempts have failed, as a result of opposition from the pharmaceutical industry and physicians (4) and because of a different legal system regarding liability.

From the experience in the European countries that fully implemented the new drug distribution model, it is clear that the public welcomes and accepts the concept of understandable written drug information (5,6). With the current legislation, however, the emphasis is heavily on risk information. European registration authorities do not accept detailed information in the insert on the benefit of the medicine, such as a paragraph on how the drug works and what it does to the symptoms of the disease for which it is prescribed. This restrictive attitude stems from the desire to protect the credibility of an authoritative text from promotional language. The current situation leads, however, to an imbalance between risk and benefit messages in patient package inserts, which may jeopardize their impact (7).

To study potential solutions to restore balance in written drug information, we conducted three parallel psychological experiments, each in a different clinical setting but with an identical design. The aim was to evaluate the effect of the insertion of benefit information into a patient package insert and to assess the impact on patients' knowledge and on the subjective benefit/risk perception of the medicine.

### MATERIAL AND METHODS

We conducted three randomized, controlled experiments in healthy volunteers, testing inserts of medicines for three different ailments. In the first experiment we tested the insert of the drug cisapride (CIS), a gastrokinetic drug for benign gastric motility disorders; in the second experiment we tested the insert of itraconazol (ITR), a fungicide for toenail infections; and in the third experiment we tested the insert of the drug risperidon (RIS), a neuroleptic drug for chronic psychosis. We selected these texts among the official inserts for their linguistic quality. We asked the responsible pharmaceutical company for per-

mission to use these inserts in this study. The study was conducted in Flanders, the Dutch-speaking part of Belgium, in 1997 to 1998.

The theoretical framework for this study (8), guiding the elaboration of study design and measurement instruments, stems from the theories of self-efficacy (9) and risk perception (10). The design of the three experiments was identical. For each experiment, we set out to select a convenience sample of 90 healthy volunteers. In experiment 1 (CIS), the volunteers were adult women recruited from community womens associations. In experiment 2 (ITR), the volunteers were adult women recruited by psychology students among their sisters and mothers. In experiment 3 (RIS), the volunteers were recruited among male or female caregivers of psychiatric patients (close relatives or partners).

Subjects were given a briefing on the nature and the purpose of the study before being asked for informed consent. Subjects were then read an introductory script (see Figure 1), to familiarize them with the clinical context of the experiment. Afterwards, subjects were randomized, using a computerized number generator, to three experimental conditions (see Figure 2):

1. A control group (CON) did not receive written medication information,
2. An intervention group (PPI) received the usual patient package insert, without benefit information, and
3. Another intervention group (BEN) received an experimental insert with a paragraph of 60 to 80 words containing benefit information (see Figure 1).

In the three experiments, we used the text of the commercially available user leaflet, written for comprehension by readers of a low-grade educational level (people who left school at 16 years of age), in 12-point type. The benefit paragraph focused on explaining drug action in experiment 1, on monitoring signs of healing in experiment 2, and on explaining the relation between the nature of the disease and drug action in experiment 3. The two intervention groups were given the

Experiment 1	<b>Cisapride in benign gastric motility disorders</b>
<p><b>Introduction script:</b> Since a few days you are feeling a bit nauseous and you lost your appetite. You experience difficulty to properly digest your food and you suffer from a bloated feeling in the stomach. Because this is really annoying, you decide to go and see the doctor. The doctor examines you and pushes on your stomach. This hurts a little bit. The doctor reassures you and gives you a prescription for [cisapride]. He tells you to take one tablet, a quarter of an hour before each meal. In case the problems would not subside, you should come and see the doctor again. After you purchased the medicine, you go home. At home you open the package.</p> <p><b>Benefit message:</b> In normal digestion ingested food flows in one direction from the mouth to the stomach and then to the digestive tube. Little muscles at the entrance and at the exit of the stomach keep the food from flowing back. Other muscles inside the stomach and in the intestines mould the food and push it further. [Cisapride] helps these little muscles to work well together. This favours a good digestion.</p>	
Experiment 2	<b>Itraconazol in fungus infection of the toe nails</b>
<p><b>Introduction script:</b> For some months now, you noticed that 3 of the five nails of your left foot show an ugly colour. This seems to get bigger and to grow towards the base of the nail. Your doctor has told you that this is an infection by fungus. The infection will not go away by itself but it will not make you ill. You agreed with the doctor that it was better to cure this infection. In the first week of next 3 months, you must take one tablet of [itraconazol] every day. Within four months you should pay a visit to your doctor to inspect your nails. After you purchased the medicine you go home. At home you open the package.</p> <p><b>Benefit message:</b> A fungus can cause infection of one or more toenails. [itraconazol] stops the growth of the fungus and kills it. Once the fungus is killed by [itraconazol], a healthy nail will grow back. The healing process takes time. Therefore, the signs of infection can still be present for a while. It can take several months before the nail looks completely healthy.</p>	
Experiment 3	<b>Risperidon in chronic psychosis</b>
<p><b>Introduction script:</b> You have taken on the task of being the daily caregiver of a psychiatric patient with chronic psychosis. This patient has been prescribed [risperidon]. This medicine needs to be taken on a daily basis, and it is your task to supervise the treatment. After you purchased the medicine you go home. At home you open the package.</p> <p><b>Benefit message:</b> Psychosis is a mental disease, in which the working of the brain is disturbed as to thinking, feeling and acting. The symptoms can be: confusion, hallucinations, distortions in hearing and sight, paranoia, feelings of anxiety and tension. [risperidon] relieves the symptoms of chronic psychosis, and helps to restore normal social function in society. It is often necessary to take the medicine continuously for a long time to suppress the signs of the disease. When treatment is stopped, symptoms can return.</p>	

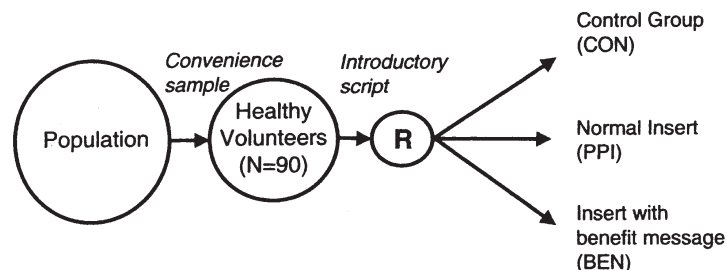
FIGURE 1. Description of introductory script and benefit message in three experiments.

opportunity to read the inserts at ease (5 to 15 minutes), while the control group was given a mock text (this was not related to the drug or disease under study, but occupied them for a comparable amount of time). Then, the inserts and mock texts were col-

lected, and a data collection booklet with measurement tests was distributed to the subjects.

To test knowledge of the drug, subjects were asked to answer 20 simple questions (edited for readers of a low-grade educational

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**FIGURE 2. Basic design of the three experimental studies.**

Randomization by random number generator

**CON:** Control group, expressing perceptions about the insert in general

**PPI:** Experimental group, after reading the normal patient package insert

**BEN:** Experimental group, after reading an insert with benefit information

level), to be answered with YES/NO/DON'T KNOW. Of the 20 questions, 16 related to the correct usage of the medicine and to the risk messages, and 4 to the experimental benefit messages. For each correct answer one point was given (potential range of results 0–20). The results of the knowledge test are presented with classical Tukey box plots (whiskers at 1.5 times box height to define outliers). Differences in sum total of correct answers were tested with the Wilcoxon signed-rank test.

Subjective benefit/risk perception of the medication was measured by a five-point bipolar Likert scale statement (the benefits of this medicine are higher than its risks), to be answered with: strongly agree, agree, neutral, disagree, or strongly disagree. Results were expressed as the percentage of subjects agreeing (strongly or moderately) with the statement, and differences were tested with the Chi<sup>2</sup> Test.

Data were collected individually (experiment 2) or in small groups of 10 to 30 subjects (experiments 1 and 3). During the experiment, contact among subjects was not allowed. The necessary sample size was calculated as 30 persons per subgroup, for a power of 80% and an  $\alpha$ -error of 0.05%, considering differences of 20% points as relevant.

## RESULTS

In the three experiments 89, 102, and 83 healthy volunteers were recruited, respectively, all of them female in experiments 1 and 2, and 60% female in experiment 3. There were no dropouts after randomization. In Table 1, details about the participating subjects are given with regard to age, educational level, and familiarity with the drug under study.

The results of the knowledge test are given in Figure 3. The scores on the knowledge test were low in the three control groups (median 1, 5, and 8 correct answers on 20 questions). Subjects from the two intervention groups (PPI and BEN) who were given written drug information scored significantly better ( $p < 0.05$  in all three experiments). The median score on 20 questions was 8 (PPI) and 9 (BEN) correct answers in the first experiment; 15 (PPI) and 16 (BEN) correct answers in the second experiment; and 14 (PPI) and 13 (BEN) correct answers in the third experiment. There were no significant differences between the two intervention groups.

The results with regard to subjective benefit/risk perception are given in Figure 4. In two of the control groups, significantly more subjects had a positive prejudice toward the benefit of medicines; 61% (ITR) and 84%

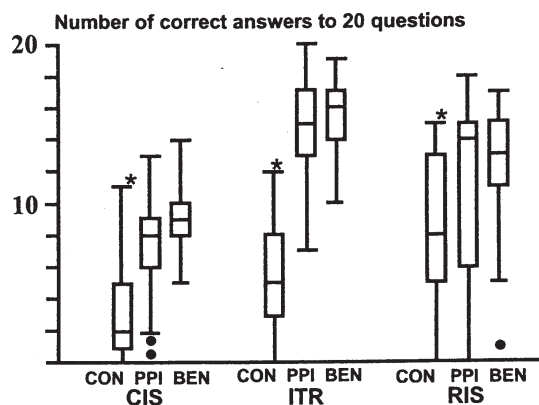
**TABLE 1**  
Description of the Subjects in the Three Experiments

	Experiment 1	Experiment 2	Experiment 3
N	89	102	83
Product	Cisapride	Itraconazol	Risperidon
Indication	Gastric motility disorders	Fungus infection of toenails	Chronic psychosis
Sex (% female)	100	100	60
Age (median, 25-75)	40(30-50)years	45(39-51)years	58(52-65)years
Educational level (% low grade)	48	31	47
Familiar with product (%)	7	10	35

(RIS) agreed that the benefit was greater, versus 41% (ITR) and 54% (RIS) of the subjects in the intervention group with the normal insert without benefit message (PPI) ( $p < 0.05$ ).

In all three experiments there was a clear difference between the two intervention

groups. More subjects in the group that read an insert with benefit information (BEN) rated the benefit higher than the risk, compared with subjects who read a normal insert (PPI) (62% vs. 31% for CIS, 64% vs. 41% for ITR, and 70% vs. 54% for RIS) ( $p < 0.05$  in all three).



**FIGURE 3. Knowledge test**

**CIS:** Experiment 1 with cisapride in gastric motility disorders

**ITR:** Experiment 2 with itraconazol in mycosis of toenails

**RIS:** Experiment 3 with risperidon in chronic psychosis

**CON:** Control group

**PPI:** Experimental group, after reading the normal patient package insert

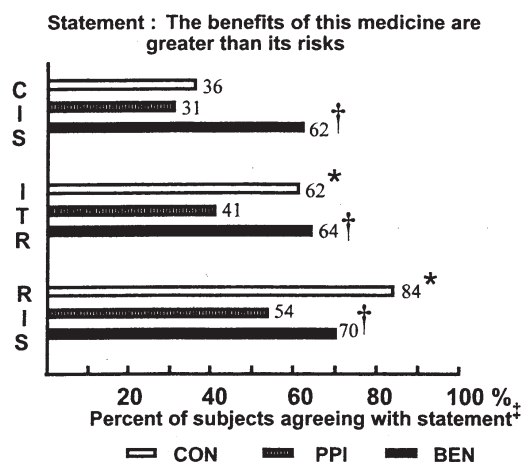
**BEN:** Experimental group, after reading an insert with benefit information

Twenty questions with 3 possible answers (YES/NO/DON'T KNOW), scored +1 for every correct answer.

Results represented with classical Tukey box plots (median, P25, P75, whiskers at max. 1.5 times box plot height to define outliers)

• Outliers

\* Significance:  $p < 0.005$ , Wilcoxon signed-rank test, testing differences between CON and (PPI or BEN)



**FIGURE 4. Subjective benefit/risk perception.**

**CIS:** Experiment 1 with cisapride in gastric motility disorders

**ITR:** Experiment 2 with itraconazol in mycosis of toenails

**RIS:** Experiment 3 with risperidon in chronic psychosis

**CON:** Control group, expressing perceptions about the insert in general

**PPI:** Experimental group, after reading the normal patient package insert

**BEN:** Experimental group, after reading an insert with benefit information

\* Significance:  $p < 0.05$ , Chi-square test, testing differences between CON and PPI

† Significance:  $p < 0.05$ , Chi-square test, testing differences between PPI and BEN

‡ % of patients agreeing (strongly or moderately) to statements in a 5-point bipolar Likert scale

## DISCUSSION

This experimental study addresses for the first time the issue of balance between risk and benefit information in patient package inserts, which are official regulatory documents in Europe. It is an exploratory study, with three small parallel experiments, enlisting healthy volunteers with different recruitment procedures and mimicking three different clinical conditions. The results cannot be extrapolated to the general population nor to patients suffering from these clinical conditions.

Our enlistment of caregivers and women was aimed at recruiting healthy volunteers with a keen interest in drug information. Previous research showed that women often play the role of gatekeeper for drug information in the family (6). The selection of caregivers of psychotic patients in experiment 3 (RIS) increased the likelihood of selecting older

volunteers and volunteers who were already familiar with the medicine. This might explain the higher score on the knowledge test of the subjects in the third control group (RIS), compared to the knowledge scores of the control groups of the two other experiments. The different recruitment procedures may have introduced a potential (positive) bias for gender and age. This may affect the generalizability of the results but not their internal validity.

In constructing our measurement tool for subjective risk/benefit perception, we chose not to separate the appraisal of risk and the appraisal of benefit in distinct Likert scales, as previous research has shown that such a separation would be artificial and contrary to cognitive processes in the patients' mind (11). Our choice of the three medications under study was pragmatic, but the clinical settings covered an acute, benign, symptomatic disease; a chronic, benign, asymptomatic

disease; and a chronic, serious, symptomatic disease.

These three experiments in different clinical settings with different recruitment procedures yielded consistent results. In the three control groups, the results of the knowledge test were worse than the results in the intervention group. This is an obvious consequence of the design and it confirms the findings of previous research on the impact of written drug information on patient knowledge (12,13). In the control groups of experiment 2 (ITR) and experiment 3 (RIS) the majority of the subjects had a positive benefit/risk perception of the drug. This was not the case in experiment 1 (CIS), where the disease might be considered to be not serious enough to be treated with medicines.

In all three experiments, at least half of the subjects with a normal insert without a benefit message indicated that the risks of the medicine exceeded the benefit. In all three experiments the insertion of a benefit message had an obvious positive impact on benefit/risk perception, as more than 60% of the patients in these groups perceived greater benefit for the medicine.

The consistency of the results in these three diverging experiments may also be interpreted as a corroboration of the robustness of the findings.

Based on these findings, we formulate the hypothesis that adding a section of benefit information within a patient package insert helps to integrate increased knowledge about medication into a more balanced subjective benefit/risk perception. More research is needed to confirm this hypothesis, and to explore its clinical relevance, for example, with regard to the impact on patient compliance (14,15).

Benefit messages in inserts for branded packages should be standardized and tested at the generic level of the active substance or therapeutic group, to reduce the workload of control for promotional claims in this section of an official document. This could encourage the European regulatory authorities to reconsider their negative attitude toward benefit information in user leaflets. Interest-

ingly, in a recent workshop organized by the United States Food and Drug Administration, the insertion of benefit information in patient package inserts was strongly advocated (16).

Adding benefit information could innovate even further the European system of distribution of medicines with understandable written information. This may help patients reach a more balanced judgment of the risk, and the benefit, of the medicine to be taken. It could heighten the value of the patient package insert as an instrument of regulatory policy (17,18,19).

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