Studies on the Expectancies Evoked by Perceptual Characteristics of Medicines - Background Factors of the Nocebo Effect

Introduction

The primary aim of the theoretical part of the thesis was a complex, critical review of the classic and modern literature of the placebo phenomenon. The definition-related problems and the theories regarding the mechanisms of the placebo effect (e.g. *expectations, conditioning, signal detection theory, meaning response*, etc.) are discussed, and the ethical concerns about the investigational and clinical usage of placebos are summarised. Possible impact of certain personality characteristics of the patient and of the perceptual characteristics (e.g. *taste, shape, size, colour*) of the medicines are discussed in details, since these factors might play an important role in the placebo effect.

In the second part, the nocebo phenomenon is discussed. Although the nocebo effect was originally defined as the adverse side effects of placebos, a broader definition is used in the current work. Nocebo effects (or non-specific side effects) are all effects that cannot be explained by the pharmacological effects of a drug. Potential mechanisms behind the nocebo effect (e.g. *classical conditioning,*

social learning, different kinds of expectations, stress, anxiety, misattribution, etc.), and the differences between the nocebo and the placebo phenomena are summarised.

Since the nocebo effect is considered as a special case of symptom reports, the most important models of symptom generation are listed, and related personality factors (e.g. *female gender, negative affectivity, introspection, somatosensory amplification, proneness to somatisation, dispositional optimism,* etc.) are discussed. The empirical evidences regarding the impact of these factors on the nocebo effect are quite poor, therefore the primary aim of this thesis has been to investigate this problem.

Our knowledge regarding the expectations and the side effects evoked by the perceptual characteristics of curatives is also scarse. Certain rules derived from the placebo-research (e.g. bigger and/or oblong shaped tablets appear to be more effective; warm colours evoke stimulant, while cold colours and the white colour generate sedative expectations and effects) seem to be applicable for the nocebo effect as well. The empirical investigation of these relationships was the second goal of the study.

In the last part, the placebo phenomenon is discussed from evolutionary point of view. According to my opinion, the placebo phenomenon is not necessarily adaptive (the nocebo effect can serve as a good example for that). It can be regarded as a by-product of other adaptive features (e.g. *learning, social lifestyle, hierarchy, etc.*).

Hypotheses

The goal of the empirical part of the current work were the investigation of the personalitiy variables behind the nocebo effect, and the study of the expectations and reactions evoked by the perceptual characteristics of medicines. The hypotheses were as follows.

Female gender and higher trait anxiety enhance the expectations regarding side effects.

Higher somatosensory amplification and somatization tendency enhance both expectations and experienced side effects, while dispositional optimism serves as a protecting factor.

Personal and family experiences with side effects and more medication induce more expectations and more side effects as well.

Enhanced expectations of side effects manifest themselves as more side effects.

Oblong-shaped tablets evoke stronger expectations, especially regarding gastrointestinal symptoms.

Warm pill colours (e.g. red, yellow) evoke stimulant-type, while cold colour (blue) and the white colour evoke sedative-type expectations and adverse side effects.

Methods

The empirical study consisted of four parts.

In the first part, the psychometric evaluation and questionnaire-based validation of the Hungarian version of the Somatosensory Amplification Scale (SSAS) was performed on a student (N=184) and a patient (N=349) sample, using the Spielberger Trait Anxiety Scale (*STAI-T*), the Patient Health Questionnaire Subjective Somatic Symptom Scale (*PHQ-15*), the Beck Depression Inventory Short Version (*BDI-R*), and the Life Orientation Test Revised Version (*LOT-R*).

In the second and third parts of the study, *expectations* of side effects and their personality background were investigated on a student (N=118) and on a patient (N=213) sample, respectively. The participants completed questionnaires (*SSAS*, *PHQ-15*, *STAI-T*, *LOT-R*, *previous personal and family experiences with drug side effects, frequency of medication*) and rated the probabilities of the occurence of ten side effects in the case of six differently looking tablets.

In the last experimental part, participants (female students, N=38) completed questionnaires (*SSAS, PHQ-15, STAI-S, LOT-R, previous experiences with drug side effects, frequency of medication, expectations*), then ingested a white or a red pill (that contained identical active substances in identical quantities), and monitored themselves for adverse effects for ten minutes.

Results and Conclusion

The Hungarian version of the Somatosensory Amplification Scale (SSAS) showed good internal consistency, and (in accordance with the international results) significant, medium level, positive correlations with trait anxiety, depression-related symptoms, and somatization tendency.

Gender and trait anxiety (*STAI-T*) were not related to *expectations* of side effects. According to the data from the literature, however, they play an important role in the generation of *symptoms*.

Both somatosensory amplification (*SSAS*) and somatization tendency (*PHQ-15*) proved to be significant predictors of the expectations of side effects and the experienced side effects as well.

Dispositional optimism (*LOT-R*) correlated neither with *expected* nor with *experienced symptom* scores.

Previous experiences and frequency of medication had no impact on expectations of side effects. Previous personal experiences, however, predicted the actual symptom score well.

There was a medium level correlation between the total expectation scores and the total symptom scores, but expectations of individual symptoms had not necessarily led to the generation of the particular symptoms.

Red pills evoked more stimulant (e.g. *agitation, irritability; palpitation*), while white pills evoked more sedative (e.g. *drowsiness, sleepiness*) expectations and symptoms, respectively. The results with yellow and blue coloured pills were rather ambiguous.

Oblong shaped tablets induced more expectations, especially regarding gastrointestinal symptoms (e.g. *nausea; diarrea; heartburn*).

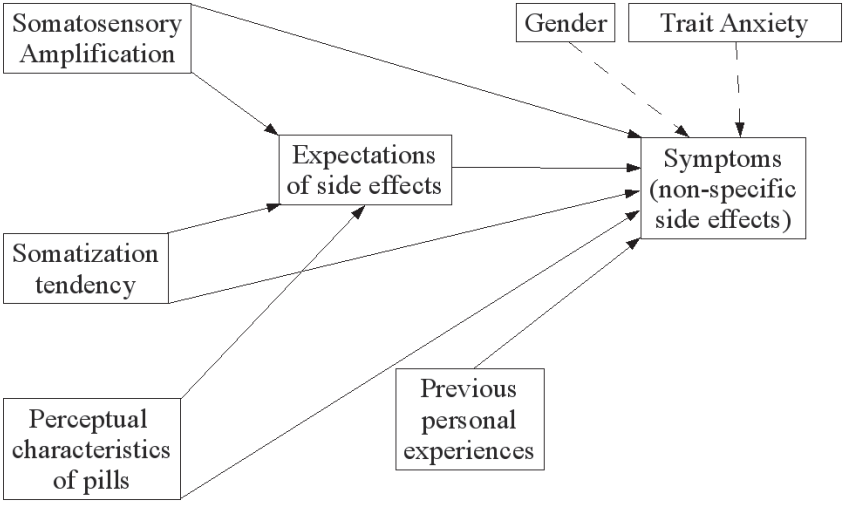

Fig 1. Summary of the results: direct and indirect ways of symptom generation.

By summarising the results, the following model was proposed (*Fig 1*). Previous personal experiences with drug side effects, and (based on literature data) gender and trait anxiety have their effects on

the generation of symptoms *directly* and not through conscious expectations (response expectancies). Somatosensory amplification, somatization tendency, and perceptual characteristics of the medicines have both *direct* and *indirect* (through expectations) impacts. Perceptual characteristics of drugs change more the quality (e.g. stimulant vs. sedative) than the total amount of the symptoms.

Expectancies evoked by perceptual characteristics of curatives can have a positive or negative impact on their effects and effectiveness, on the patients' compliance, and on the total outcome of the therapy as well. These factors should be taken into consideration in the process of choosing the look-and-feel of the medicines (*intelligent medicine designing*).

A proportion of adverse side effects of drugs is of non-specific origin, and the existence of nocebo effects can be *presumed* based on certain personality factors. For the treatment of these effects and patients, a *special therapeutic strategy* (e.g. gradually increased dosage, patient education, etc.) is needed.

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