Seeing Is Believing: Impact of Social Modeling on Placebo and Nocebo Responding

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Objective: This study investigated the impact of the social modeling of side effects following placebo medication ingestion on the nocebo and placebo effect. It also investigated whether medication branding (brand or generic labeling) moderated social modeling effects. Method: Eighty-two university students took part in the study which was purportedly investigating the impact of fast-acting beta-blocker medications (actually placebos) on preexamination anxiety. After taking the medication, participants were randomized to either witness a female confederate report experiencing side effects or no side effects after taking the same medication. Differences in symptom reporting, blood pressure, heart rate, and anxiety were assessed between the social modeling of side effects and no modeling groups. Results: Seeing a female confederate report side effects reduced the placebo effect in systolic (p = .009) and diastolic blood pressure (p = .033). Seeing a female confederate report side effects also increased both total reported symptoms (mean [SE] 7.35 [.54] vs. 5.16 [0.53] p = .005) and symptoms attributed to the medication (5.27 [0.60] vs. 3.04 [0.59] p = .01), although the effect on symptoms was only seen in female participants. Females who saw the confederate report side effects reported approximately twice the number of symptoms as those in the no modeling group. Social modeling did not affect heart rate or anxiety. Medication branding did not influence placebo or nocebo outcomes. Conclusions: The social modeling of symptoms can substantially reduce or eliminate the placebo effect. Viewing a female confederate display symptoms after taking the same medication increases symptom reporting in females.

Keywords: placebo, nocebo, social modeling, side effects, symptoms

Medication use in daily life occurs within a social context that is often overlooked or deliberately eliminated in randomized controlled trials of placebo and nocebo effects. In daily life, and particularly when starting a new treatment or switching medications, patients are likely to talk with others in person and via the many patient support and drug information Web sites about how effective (or not) their treatment is and what side effects they are experiencing, especially if they have concerns about the medication. Such Web sites may provide a form of technologically mediated social modeling, and many drug information sources list exceptionally large numbers of possible medication side effects for commonly used drugs (Tan, Petrie, Faasse, Bolland, & Grey, 2014).

In the context of a medication scare, hearing about symptoms in people taking the same medication can exacerbate anxiety and increase the reporting of these same symptoms. An example of the potential impact of social modeling in a health scare came from the Eltroxin formulation change scare in New Zealand (Faasse, Cundy, & Petrie, 2009), in which the modeling of symptoms through Web site discussion boards and the news media increased patient anxiety and the reporting of adverse drug events (Faasse et al., 2009; Faasse, Gamble, Cundy, & Petrie, 2012).

Recent evidence also indicates that social observation plays an important role in both placebo and nocebo responding (Benedetti, 2013). Evidence from a small number of studies points to the importance of the social context in general, and social modeling by another person specifically, on placebo responding. Seeing another participant (actually a study confederate) report pain reduction under certain study conditions results in placebo analgesia in the viewer (Colloca & Benedetti, 2009). This is true even if the confederate is viewed in a prerecorded video clip (Hunter, Siess, & Colloca, 2013).

The nocebo effect is less well known than the placebo effect. The nocebo effect occurs when expecting to experience unpleasant side effects results in these symptoms being experienced after taking an inert medication or placebo (Barsky, Saintfort, Rogers, & Borus, 2002). Nocebo effects can also occur following social modeling. Seeing a confederate report side effects after inhaling a placebo described as a potentially toxic substance increases the number of symptoms reported (Broderick, Kaplan-Liss, & Bass, 2011), and this effect appears to be more pronounced in female participants (Lorber, Mazzoni, & Kirsch, 2007). Even the presence of a person of the same gender, whether there is social modeling...
or not, can increase the reporting of physical symptoms in both sexes (Mazzoni, Foan, Hyland, & Kirsch, 2010).

Current evidence indicates that the modeling of improvement can induce placebo effects, and that modeling of side effects can induce nocebo effects. However, medication effectiveness and side effects tend to be linked in the way patients think about medicine (McHorney, Schousboe, Cline, & Weiss, 2007). The experimental paradigms used to investigate these effects up to this point have typically not enabled the investigation of any crossover effects from the modeling of side effects to the placebo effect.

Results of previous studies indicate the importance of social modeling in both placebo and nocebo effects, and such modeling has been shown to influence real-world medication outcomes. However, these studies have not investigated the impact of the modeling of side effects on placebo effects. The aim of the current study was to investigate the impact of the social modeling of side effects on both the nocebo effect and the placebo effect following the administration of a placebo tablet described as a beta-blocker medication. A similar paradigm not involving social modeling has previously been successfully utilized by the research group to investigate the impact of a medication change on placebo and nocebo effects and shown a reliable placebo effect on blood pressure (Faasse, Cundy, Gamble, & Petrie, 2012). The role of medication branding (brand name or generic labeling) in moderating social modeling effects was also investigated.

**Materials and Method**

**Design**

Participants were recruited to take part in a study which was purportedly investigating the impact of fast-acting beta-blocker medications on preexamination anxiety. In reality, all tablets were placebos. Participants were randomly assigned to one of two social modeling conditions (a female confederate who either did or did not report medication side effects), and half of each modeling group was randomly assigned to one of two medication branding conditions. This resulted in four groups: those who received a brand name tablet and experienced the social modeling of side effects; those who received a generic labeled tablet and experienced the social modeling of side effects; those who received a brand name tablet and did not see the actor model side effects; and those who received a generic labeled tablet and did not see the actor model side effects. We estimated that the minimum required sample size was 80 participants (20 in each group) to achieve 80% power at a 0.05 significance level. This was based on achieving a 20% clinically significant main effect difference in the number of symptoms reported by the groups using a 2 × 2 between-subjects factorial design. Participants were fully debriefed following the conclusion of data collection. Ethical approval for the study was obtained from the University of Auckland Human Participants Ethics Committee on February 22, 2013 (reference number 9094).

**Participants**

Participants were undergraduate students from The University of Auckland recruited using posters placed around the university campus and e-mail messages sent out to undergraduate students enrolled in medicine, nursing, law, psychology, and engineering courses. In total, 82 participants took part in this research. The sample consisted of 41 females and 41 males, with a mean age of 21 years (SD = 2.69). The majority of participants identified as being of European ethnicity (55%). In total, 107 students expressed interest in taking part. Inclusion criteria required participants to be 18 years of age or over, and able to read and write in English. Potential participants were excluded if they had an asthma diagnosis, or their blood pressure readings at baseline were under 100/60 mmHg. Four were screened out because they were ineligible to participate either because they had asthma or their blood pressure was too low. The remaining 21 did not book an appointment to participate in the study. A consort diagram for the study is presented in Figure 1.

**Procedure**

All participants attended one 1-hr research session. Blood pressure and heart rate were assessed twice prior to medication ingestion (after verbal information about the study was provided and written consent to take part in a beta-blocker study was obtained, and after completion of the baseline questionnaire), and twice after participants believed the medication had had time to take effect (immediately following the waiting period, and again before completing a brief exam simulation).

Following the completion of baseline physiological and questionnaire measures, a second researcher gave each participant standardized verbal information about the medication and possible side effects. Participants were told that the beta-blocker tablet contained 50 mg of the active ingredient metoprolol, would take 10 to 15 min to take effect, and that the medication would lower their blood pressure and heart rate, as well as helping them to feel more relaxed and calm. Participants were informed that they may experience a number of mild medication side effects: headache, feeling tired or drowsy, feeling dizzy or lightheaded, getting a sore throat, dry mouth, skin itching, unusually cold hands or feet, and nausea or stomach pain.

The primary researcher was not present for the medication administration and was blind to both the medication that participants received (brand or generic labeled) and whether they saw a female described as another study participant (actually a confederate) report medication side effects (social modeling of side effects) or not. Following the medication administration, participants were told that they would be taken to a waiting area for the 15-min waiting period while the medication took effect. The confederate was already in the waiting area when the participant arrived. Participants were informed that the beta-blocker tablets would take effect within approximately 10 to 15 min. The second researcher asked both the confederate and the participant how they were feeling 10 min after tablet ingestion. In the no modeling of side effects condition the confederate reported feeling “fine.” In the social modeling condition the confederate reported experiencing four side effects (headache, dizziness, drowsiness, and dry mouth). The confederate was always asked how they were feeling before the study participant.

After 15 min, the primary researcher collected the participant to continue with the study session. The participant then completed a brief cognitive task purportedly to assess exam performance. Following this, participants completed measures assessing their self-reported state anxiety levels, as well as any symptoms that they
had experienced since taking the study tablet, and questions about whether they believed that these symptoms were caused by the medication that they had taken.

**Measures**

**Blood pressure and heart rate** were assessed by the primary experimenter who was blind to group allocation using a Spacelabs ambulatory blood pressure monitor with a standard cuff size. Baseline readings were taken before participants took the medication, 5 and 10 min after the beginning of the study session. The mean of these readings was calculated to give baseline blood pressure and heart rate values. A postmedication value was calculated from mean of the two readings taken 15 and 20 min after participants took the study tablet. Systolic and diastolic blood pressure and heart rate change scores were calculated by subtracting the baseline score from the postmedication score.

**Physical symptoms** were assessed using a modified version of the Subjective Health Complaints Scale (Eriksen, Ihlebaek, & Ursin, 1999), with the addition of the symptoms that participants had been informed were possible mild side effects of the medication. At baseline, participants were asked to what degree (not present, mild, moderate, or severe) they had experienced each of the 39 symptoms, including tiredness, heartburn, and neck pain, during the past 30 min. Participants completed the same symptom questionnaire 30 min after taking the study tablets. At this time they were also asked whether they thought the symptoms they had experienced were medication side effects. Participants were asked to rate their experience of the intensity of 39 symptoms on a scale from 0 (not present) to 3 (severe). Symptoms were dichotomized as “present” or “not present” and total scores were calculated by summing the number of symptoms reported after participants took the tablets, and the number of symptoms that participants attributed to medication side effects.

**State anxiety** was assessed with the short-form state scale of the Spielberger State–Trait Anxiety Inventory (Marteau & Bekker, 1992). This scale contains six items, including I am tense and I feel calm which are summed to give an overall score. The scale scores range from 6 (not at all anxious) to 24 (extremely anxious). Participants were low in state anxiety at baseline, with a mean of 9.34 (SD = 2.41). Participants completed the short-form state anxiety inventory twice during the study session: at baseline and approximately 30 min after they ingested the study tablet. State anxiety change scores were calculated by subtracting the baseline score from the postmedication score.

**Statistical Analysis**

All statistical analyses were conducted using SPSS version 22. Analysis of variance (ANOVA) and chi square tests were used to investigate whether there were any baseline differences between the groups. The main effects of social modeling and medication labeling, as well as the interaction of these two factors were investigated using analysis of covariance (ANCOVA). The gender of the participant was also included as a factor in the models because a previous study found that social modeling of symptoms
influenced symptom reporting in female participants only (Lorber et al., 2007). Outcome measures were change in systolic and diastolic blood pressure, change in heart rate, change in state anxiety, and number of symptoms reported after medication and number of symptoms attributed as medication side effects. Baseline values for each of the outcome variables were included in the relevant model as covariates. Significant interaction effects were further investigated using post hoc tests with a Bonferroni correction. An alpha level of .05 was used for all other tests.

**Results**

The experiment was designed to investigate the impact of seeing another participant (actually a confederate) report medication side effects on placebo (blood pressure, heart rate, and state anxiety reduction) and nocebo (reported symptoms and medication side effects) responding following the administration of a brand name or generic labeled placebo tablet (described as a fast-acting beta-blocker medication). There were no significant differences between the four groups in age, sex, ethnicity, or reported GP visits during the previous year. In addition to this, there were no significant differences between the groups at baseline in self-reported state anxiety, symptoms experienced during the past half hour, systolic and diastolic blood pressure, or heart rate.

**Blood Pressure, Heart Rate, and Anxiety**

There was a significant main effect of social modeling on changes in systolic and diastolic blood pressure, with participants who did not see the confederate report side effects demonstrating significantly larger decreases in blood pressure ($M_{sys} = -5.30$ mmHg, $SE = 0.90$, 95% CI [−7.10, −3.50]; $M_{dia} = -2.94$ mmHg, $SE = 0.91$, 95% CI [−4.74, −1.13]) than those participants who saw the confederate report experiencing medication side effects ($M_{sys} = -1.86$ mmHg, $SE = 0.91$, 95% CI [−3.67, −0.04]; $M_{dia} = -0.13$ mmHg, $SE = 0.91$, 95% CI [−1.95, 1.69]). $F_{sys}(1, 73) = 7.22, p = .009$, partial $\eta^2 = .09$, $F_{dia}(1, 73) = 4.74, p = .033$, partial $\eta^2 = .06$ (see Figure 1). There was no significant impact of medication branding on changes in blood pressure, nor was there a significant sex effect. Similarly, there were no significant interaction effects between social modeling, medication branding, or sex. Furthermore, there was no significant effect of social modeling, medication branding, or sex on changes in heart rate or state anxiety, nor were there any significant interaction effects between these factors.

**Total Symptoms and Attributed Medication Side Effects**

There was a significant main effect of the social modeling on both the total number of symptoms reported after medication and the number of symptoms attributed as medication side effects. Participants who saw the confederate report side effects reported significantly more total symptoms and side effects ($M_{tot} = 7.35$, $SE = 0.54$, 95% CI [6.28, 8.42]; $M_{se} = 5.27$, $SE = 0.60$, 95% CI [4.08, 6.47]) than those who did not see the confederate report side effects ($M_{tot} = 5.16$, $SE = 0.53$, 95% CI [4.10, 6.22]; $M_{se} = 3.04$, $SE = 0.59$, 95% CI [1.86, 4.23]), $F_{tot}(1, 73) = 8.36, p = .005$, partial $\eta^2 = .10$, $F_{se}(1, 73) = 6.99, p = .010$, partial $\eta^2 = .09$.

There was also a significant main effect of sex on the total number of symptoms and side effects reported after medication, with females reporting significantly more total symptoms and side effects ($M_{tot} = 7.43$, $SE = 0.54$, 95% CI [6.36, 8.50]; $M_{se} = 5.22$, $SE = 0.60$, 95% CI [4.03, 6.41]) than males ($M_{tot} = 5.08$, $SE = 0.53$, 95% CI [4.02, 6.14]; $M_{se} = 3.09$, $SE = 0.60$, 95% CI [1.90, 4.28]), $F_{tot}(1, 73) = 9.65, p = .003$, partial $\eta^2 = .12$, $F_{se}(1, 73) = 6.37, p = .014$, partial $\eta^2 = .08$ (see Figure 3). There was not a significant main effect of medication branding on total symptom reporting or attribution of side effects.

There was a significant interaction effect between social modeling and sex, $F_{tot}(1, 73) = 9.70, p = .003$, partial $\eta^2 = .12$, $F_{se}(1, 73) = 4.48, p = .038$, partial $\eta^2 = .06$ (see Figure 2). Males who saw the confederate report side effects did not report experiencing any more total symptoms or side effects ($M_{tot} = 5.00$, $SE = 0.73$, 95% CI [3.55, 6.45]; $M_{se} = 3.31$, $SE = 0.81$, 95% CI [1.70, 4.93]) than those who did not see the confederate report side effects ($M_{tot} = 5.16$, $SE = 0.78$, 95% CI [3.61, 6.72]; $M_{se} = 2.87$, $SE = 0.87$, 95% CI [1.13, 4.60]), $F_{tot} = .88, p_{se} = .71$, yet females who saw the confederate report side effects reported approximately twice the number of symptoms and side effects ($M_{tot} = 9.70$, $SE = 4.74$, $SE = 0.91$, 95% CI [−4.74, −1.13]) than those who did not see the confederate report side effects ($M_{tot} = 5.16$, $SE = 0.78$, 95% CI [3.61, 6.72]; $M_{se} = 2.87$, $SE = 0.87$, 95% CI [1.13, 4.60]), $F_{tot} = .88, p_{se} = .71$, yet females who saw the confederate report side effects reported approximately twice the number of symptoms and side effects ($M_{tot} = 9.70$, $SE = 4.74$, $SE = 0.91$, 95% CI [−4.74, −1.13]) than those who did not see the confederate report side effects ($M_{tot} = 5.16$, $SE = 0.78$, 95% CI [3.61, 6.72]; $M_{se} = 2.87$, $SE = 0.87$, 95% CI [1.13, 4.60]), $F_{tot} = .88, p_{se} = .71$, yet females who saw the confederate report side effects reported approximately twice the number of symptoms and side effects ($M_{tot} = 9.70$, $SE = 4.74$, $SE = 0.91$, 95% CI [−4.74, −1.13]) than those who did not see the confederate report side effects ($M_{tot} = 5.16$, $SE = 0.78$, 95% CI [3.61, 6.72]; $M_{se} = 2.87$, $SE = 0.87$, 95% CI [1.13, 4.60]), $F_{tot} = .88, p_{se} = .71$, yet females who saw the confederate report side effects reported approximately twice the number of symptoms and side effects ($M_{tot} = 9.70$, $SE =
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more stoic, and thus any symptoms reported may be interpreted as 2013). This may be because males are perceived as normatively a larger influence than a female confederate (Swider & Babel, and the nocebo effect suggests that a male confederate may have match/mismatch effect. Further, research into social observation males or whether the results reflect a participant-confederate sex- whether females are more influenced by social modeling than same sex confederate. It remains unclear from the current study reporting following social modeling, in particular in females following modeling by a female confederate, or in the presence of a low heart rate (Faasse et al., 2012). Unlike the previous study, no placebo effect differences were seen in blood pressure but not mention side effects can influence the placebo effect as well as the nocebo effect. Importantly, these effects were not limited to self-reported outcomes, but also physiological changes in systolic and diastolic blood pressure. At a population level, a 5 mmHg reduction in systolic (or diastolic) blood pressure reduces relative risk of mortality from vascular disease by about 13% (Lewington, Clarke, Qizilbash, Peto, & Collins, 2002). In line with previous work, placebo effect differences were seen in blood pressure but not heart rate (Faasse et al., 2012). Unlike the previous study, no differences in placebo responding in self-reported state anxiety were found in the current research. This may be because participants in the current study reported very low levels of state anxiety at baseline, making it difficult to detect a placebo effect on anxiety.

The current findings with regard to symptom reporting are also in line with those of Mazzoni and colleagues (Lorber et al., 2007; Mazzoni et al., 2010), which demonstrated increased symptom reporting following social modeling, in particular in females following modeling by a female confederate, or in the presence of a same sex confederate. It remains unclear from the current study whether females are more influenced by social modeling than males or whether the results reflect a participant-confederate sex-match/mismatch effect. Further, research into social observation and the nocebo effect suggests that a male confederate may have a larger influence than a female confederate (Swider & Babel, 2013). This may be because males are perceived as normatively more stoic, and thus any symptoms reported may be interpreted as more serious by an observer. A male confederate in the current study may have had a larger effect, and replication under these conditions is warranted.

The important question is why seeing another “participant” report medication side effects significantly reduced or eliminated the placebo effect in the social modeling group, as well as enhancing the nocebo effect in female participants. There seem to be two possible explanations. First, it may be that side effects are seen as an indicator of drug quality and therefore that drugs that have a number of side effects are less effective. Viewing someone else report adverse effects may therefore influence participants’ expectations about both the likelihood of side effects and medication efficacy, increasing the probability of experiencing nocebo effects, and reducing the placebo effect. Such altered expectations could have played a role in the differences in placebo and nocebo effects seen between the two social modeling conditions. This could be investigated using a similar study design to the current research, with additional assessment of participants’ expectations about drug efficacy and the likelihood of experiencing side effects.

Another possible mechanism is attention or distraction. Witnessing the confederate report side effects may have directed participants’ attention toward monitoring their own body for the modeled side effects, and away from focusing on the expected outcome of the medication. The increase in symptoms in the social modeling group and lack of a placebo effect may reflect a switch in attention, in the face of a health threat, to focus on whether they were experiencing the same symptoms as the confederate. A similar social modeling study protocol utilizing a cognitive attention task may provide evidence about the role of attention in the social modeling of side effects.

There are important clinical implications from the current study. First, female participants who observed the female confederate report side effects reported twice the number of symptoms after taking the medication compared to those who were not in the social modeling condition. The experience of physical symptoms, including those due to the nocebo effect, is an important driver of health care seeking (Petrie, Faasse, Crichton, & Grey, 2014; Verbrugge, 1985). Symptoms that are attributed to medication side

**Figure 3.** Bar graph showing the interaction effect between participant sex and social modeling on total symptom reporting and symptoms attributed to medication side effects.

<table>
<thead>
<tr>
<th>Participant Sex</th>
<th>No Modeling</th>
<th>Modeling</th>
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</thead>
<tbody>
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<td></td>
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<tr>
<td>Female</td>
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<table>
<thead>
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<th>Symptom Reporting</th>
<th>Male</th>
<th>Female</th>
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</thead>
<tbody>
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<td></td>
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<tr>
<td>Modeling</td>
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Total Number of Symptoms Reported

- Male: $M_{tot} = 7.23, SE = 0.88, 95% CI [5.47, 8.99]$
- Female: $M_{tot} = 3.22, SE = 0.81, 95% CI [1.61, 4.82]$

**Discussion**

The results of the current study demonstrate that the social modeling of symptoms can substantially reduce the placebo effect on blood pressure in both males and females, and also increase the nocebo effect in terms of reported symptoms and medication side effects in female participants. To the authors’ knowledge, this is the first study to demonstrate that the social modeling of medication side effects can influence the placebo effect as well as the nocebo effect. Importantly, these effects were not limited to self-reported outcomes, but also physiological changes in systolic and diastolic blood pressure. At a population level, a 5 mmHg reduction in systolic (or diastolic) blood pressure reduces relative risk of mortality from vascular disease by about 13% (Lewington, Clarke, Qizilbash, Peto, & Collins, 2002). In line with previous work, placebo effect differences were seen in blood pressure but not heart rate (Faasse et al., 2012). Unlike the previous study, no differences in placebo responding in self-reported state anxiety were found in the current research. This may be because participants in the current study reported very low levels of state anxiety at baseline, making it difficult to detect a placebo effect on anxiety.

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There are important clinical implications from the current study. First, female participants who observed the female confederate report side effects reported twice the number of symptoms after taking the medication compared to those who were not in the social modeling condition. The experience of physical symptoms, including those due to the nocebo effect, is an important driver of health care seeking (Petrie, Faasse, Crichton, & Grey, 2014; Verbrugge, 1985). Symptoms that are attributed to medication side
effects can result in medication nonadherence or discontinuation, as well as increased costs associated with additional medical consultations, medication switches, or drugs to manage side effects (Barsky et al., 2002). Increased medication side effects following social observation have the potential to increase medical visits, as well as impact treatment adherence and other treatment decisions (Petrie & Weinman, 2012). Additionally, a reduction in medication efficacy due to a diminished placebo effect following social observation of symptoms may result in the need for an increased dose of active ingredient in order to maintain the clinical effect of the drug.

The current study is limited by the nature of the sample, who were predominately healthy university students. The research was strengthened by the blinding of the primary experimenter to the assigned condition of the participants. Additionally, the cover story was well suited to the participant population, with no student questioning the purported study rationale. Further research is warranted to investigate the generalizability of the current findings to a broader participant group. It is also worth noting that the effects of social modeling on symptoms were assessed following a brief exposure to the confederate (15 min) and in a medication that participants took only once. It may be that there are greater effects after a longer period of time, in medications that are part of patients’ daily life, or when the symptoms modeled are more dramatic and extreme.

The findings of the current study have potential implications for the efficacy and side effects of all medicines and medical treatments. Information about medication side effects is widely available on the Internet, and health and medicines are commonly discussed over the Internet, in the news media, and in interpersonal communication between patients (Faasse et al., 2012; Faasse et al., 2009; Tausczik, Faasse, Pennebaker, & Petrie, 2012). There is the potential for such forms of social modeling of medication side effects to increase the experience of symptoms in patients as well as reducing treatment efficacy due to a reduced placebo component.

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