Remotely provided open-label placebo reduces frequency of and impairment by allergic symptoms

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April 16, 2024

Abstract

Background: Placebos being prescribed with full honesty and disclosure (i.e., open-label placebo = OLP) have been shown to reduce symptom burden in a variety of conditions. With regard to allergic rhinits, previous research provided inconclusive evidence for the effects of OLP, possibly related to a separate focus on either symptom severity or symptom frequency. Overcoming this limitation of previous research, the present study aimed to examine the effects of OLP on both the severity and frequency of allergic symptoms. **Methods**: In a randomized-controlled trial, patients with allergic rhinits (N=74) were randomized to OLP or treatment as usual (TAU). Due to the COVID-19 pandemic, OLP was administered remotely in a virtual clinical encounter. Participants took placebo tablets for 14 days. The primary outcomes were the severity and frequency of allergic symptoms. The secondary endpoint was allergy-related impairment. **Results**: OLP did not significantly improve symptom severity over TAU, $F(1, 71) = 3.280$, $p = .074$, $\eta^2_p = .044$, but did reduce symptom frequency, $F(1, 71) = 7.272$, $p = .009$, $\eta^2_p = .093$, and allergy-related impairment more than TAU, $F(1, 71) = 6.445$, $p = .013$, $\eta^2_p = .083$, reflecting medium to large effects. The use of other anti-allergic medication did not influence the results. **Conclusions**: While OLP was able to lower the frequency of allergic symptoms and allergy-related impairment substantially, its effects on symptom severity were weaker. The remote provision of OLP suggests that physical contact between patients and providers might not be necessary for OLP to work.

Introduction

Allergic rhinitis causes symptoms such as sneezing, runny nose or itchy eyes, which are especially prevalent in the pollen season[1]. Such symptoms of allergic rhinitis can be reduced by some available medications; however, these medications often have side effects, and the results from placebo-controlled clinical trials suggest that symptom improvement is largely driven by the placebo response [2-5]. This raises the question of whether allergic symptoms can be reduced by placebos, which usually do not have any side effects. The placebo response is known to contribute to symptom reduction in a variety of conditions, based on psychobiological mechanisms such as expectations, learning, and patient-provider interaction [6-8]. It has been believed that placebo effects are based on the patients' false belief of receiving active medication. In recent years, however, a growing body of research has demonstrated that placebos being prescribed to patients with full honesty and transparency (referred to as "open-label placebos" = OLPs) improve symptoms in irritable bowel syndrome [9,10], chronic back pain [11-13], migraine[14], cancer-related fatigue [15,16], depression [17,18], test anxiety [19], and other conditions [20]. With respect to allergic rhinitis, though, there is inconclusive evidence regarding the effectiveness of OLP.

In two small samples of people with allergic rhinitis, Schäfer et al. found that OLP significantly reduced the frequency of allergic symptoms in comparison to treatment as usual (TAU) [21,22]. In another study with a slightly larger sample size, OLP failed to improve the severity of symptoms of allergic rhinitis [23]. These studies differed in two important respects. First, in the studies by Schäfer et al., OLP was administered in a clinical encounter with physical contact [21,22], whereas in the study by Kube et al. [23], OLP had to be provided remotely (i.e., through a virtual encounter) due to the COVID-19 pandemic. The second difference pertains to different measures used for the assessment of allergic symptoms. While Schäfer et al. used a questionnaire assessing a broad variety of allergic symptoms [21,22], Kube et al. followed the recommendations of regulatory authorities[24] to use a short scale that assesses only symptoms related to eyes and nose [23]. In addition, the two measures differed in so far as the former assesses the frequency of allergic symptoms, whereas the latter assesses symptom severity.

Drawing on that previous research, the present study sought to examine the effects of OLP on symptoms of allergic rhinitis. Specifically, we compared the effects of OLP plus TAU with TAU alone in a randomized-controlled trial (RCT). The primary endpoint was symptoms of allergic rhinitis. To address different assessment approaches as a potential explanation of the discrepant results in previous research[21-23], the current study applied both previously used measures to assess both the severity and the frequency of allergic symptoms. The secondary endpoint was the degree of impairment caused by allergic symptoms. Based on the results of previous research[23], we also examined whether the effects of OLP are modulated by current anti-allergic medication.

Methods

The study was conducted at two German universities and the Institutional Review Board of both sites approved the study (reference numbers 2020_236 and 2021-JGU-psychEK-001). The study was conducted in accordance with ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. All participants gave informed consent. The study was pre-registered on AsPredicted.org: https://aspredicted.org/9F8_BZ5.

Participants

Participants were recruited via email lists, public postings, newspaper announcements, and social media. The inclusion criteria were: diagnosed allergic rhinitis; at least 18 years old; and sufficient German language skills. As with previous studies [21-23], exclusion criteria were: pregnancy; diabetes; any mental or neurological illness; and lactose intolerance (since the placebo tablets contained lactose). Of note, we did not apply any restrictions regarding the intake of participants' normal medication (if there was any), but participants were asked not to change their medication (or dosages) for the duration of the study.

We recruited participants during the pollen season, with the first participant being enrolled in late April and the last participant being enrolled in mid-August. In this period, we aimed to reach a sample size of 90 participants to be able to uncover medium effects of OLP ($f = .30$; $\alpha = .05$; 1-$\beta = .80$). A total of 123 people expressed interest in the study, of whom 96 persons completed a feedback form and were screened for eligibility. Of these, 74 people were randomized to OLP+TAU (subsequently referred to as "OLP") or TAU. A total of 72 people completed the study at follow-up, as detailed in the CONSORT diagram (see Figure 1).

Insert Figure 1 here.

In the entire sample, the mean age was 32.4 years ($SD = 13.0$) and 73.0% of the participants were female (27.0% male). All other sociodemographic data and information on medication use is presented for the two treatment groups separately in Table 1. There were no significant baseline differences between the groups.

Insert Table 1 here.

Procedure

If participants were included in the study, the experimenter randomized participants to OLP vs. TAU (see Figure 2). Accordingly, participants were sent a concealed envelope with either placebo tablets for those randomized to OLP or "smarties" (i.e., color-varied sugar-coated chocolate confectionery) for those randomized to TAU in a small glass container (see supplement) and were asked not to open the envelope before the first study visit a few days later (T1). Due to the COVID-19 pandemic, the study visit took place online, using the video platform www.arztkonsultation.de, which is widely used in Germany because of its strict data safety policy. In the virtual encounter, we aimed to ensure a warm and competent clinical encounter through both verbal and non-verbal elements [25,26].

In the first study visit, the provider explained the administration of OLP to the participants. In so doing, we closely adhered to previous studies administering OLP [9,11,15,17,19,21,22,27,28]. Using the survey platform www.soscisurvey.de, participants were subsequently asked to complete questionnaires regarding their expectancies and hopes for placebo treatment as well as the extent to which they felt informed about placebos. Furthermore, participants completed questionnaires assessing their current allergic symptoms and the degree of impairment caused by allergic symptoms. After completing the questionnaires, participants were asked to open the envelope with the placebo tablets or smarties. At this point, participants were informed about their treatment group allocation, and potential ensuing questions were discussed. Finally, an appointment was made for the follow-up visit 14 days later (T2). Of note, unlike a previous study on the remote provision of OLP [23], we decided to send participants the placebo tablets or smarties prior to the first appointment, since the previous study discussed the delay between the explanation of OLP and participants' reception of placebo tablets a few days later as a potential reason for the failure of OLP as patients may have been no longer aware of the potential benefits of placebos when starting to take them.

At T2, the provider asked participants to complete the follow-up questionnaires for their allergic symptoms. Afterwards, the provider asked participants how they experienced taking the placebo and whether they noticed any beneficial or adverse effects. Participants from the TAU group were offered the possibility of taking placebos after the second appointment ("switch-over"). Of 38 participants from the TAU group, 22 persons decided to receive the placebos subsequently. In terms of the intake of placebos, participants from the TAU group received the same information as participants from the OLP group at T1. Participants from the TAU group who wanted to receive placebos were invited for a third virtual appointment (T3), ˜17 days later due to the delay of the postal service delivering the placebos. At T3, participants completed the symptom questionnaires again and the provider asked for beneficial and adverse effects of the placebos, as described above.

At each site, the appointments were conducted by a female psychology Master's student, based on a structured interview guide following the procedure of a previous study [23]. The background visible in the online interview was kept constant across all interviews and study sites in the form of a clean white wall.

Insert Figure 2 here.

Measures

Allergic Symptoms

The primary outcome of the present study was self-reported symptoms of allergic rhinitis. To this end, we applied two previously used measures. First, we used the Combined Symptom Medication Score (CSMS). This 6-item scale assesses symptoms of allergic rhinitis in the past 2 weeks, related to the nose (four items) and the eyes (two items). Each item (reflecting a particular symptom) is rated on a 4-point Likert scale, indicating the severity of symptoms (from 0 = "no symptoms" to 3 = "severe symptoms"). Of note, the CSMS can also be used to compute a medication score; however, as participants in the current study were required not to change their medication during the study period (resulting in a constant that would have been added to the symptom score), the medication score was not used and participants rated only the

symptom-related items. At T1, Cronbach's alpha of the CSMS was $\alpha = .70$; at T2 it was $\alpha = .82$; and at T3 it was $\alpha = .87$.

In addition, we used the 30-item questionnaire developed by Schäfer et al. [21,22] that, unlike the CSMS, assesses not only eye-related and nose-related symptoms, but also focuses on additional symptoms that people with allergic rhinitis typically experience in the pollen season, such as skin irritations, problems with breathing, and more general symptoms such as tiredness. In contrast to the CSMS, the allergy questionnaire by Schäfer et al. does not assess the*severity* of allergic symptoms, but the *frequency* of their occurrence, ranging from 1 ("never") to 7 ("always"). Like the CSMS, it also refers to the experience of allergic symptoms in the past 2 weeks. At T1, Cronbach's alpha of that scale was $\alpha = .92$; at T2 it was $\alpha = .93$; and at T3 it was $\alpha = .92$. The intercorrelation of the CSMS with the symptom frequency scale by Schäfer et al. was $r = .621$ ($p < .001$) at T1, $r = .765$ ($p < .001$) at T2, and $r = .864$ ($p < .001$) at T3.

Impairment

As a secondary outcome measure, allergy-related impairment in quality of life was assessed using the short form of the Rhinitis/Rhinoconjunctivitis Quality of Life Questionnaire. This is the German translation of the Mini Rhinoconjuctivitis Quality of Life Questionnaire (MiniRQLQ) [29]. Through 14 items, the MiniRQLQ assesses the degree of impairment caused by allergy-related symptoms. Two items refer to practical problems (e.g., "having to rub nose or eyes") and three items each refer to limitations in activities (e.g., "sleep [difficulty sleeping through the night and/or falling asleep at night]"), nasal symptoms, eye symptoms and other complaints (e.g., "irritability"). Respondents indicate the degree of impairment for each item on a seven-point Likert scale (0 = "not at all" to 6 = "extremely"). The instruction was slightly adapted so that the items referred to the last 14 days, instead of the last 7 days, to ensure comparability with the primary endpoint. The MiniRQLQ is a reliable and valid questionnaire that is sensitive to symptom changes[29,30]. Cronbach's alpha was $\alpha = .90$ at T1, $\alpha = .91$ at T2 and $\alpha = .90$ at T3.

Medication Use

To assess whether participants took any medication against their allergic symptoms, they were asked to choose one of three options: 1) "I regularly take medication against my allergic symptoms"; 2) "I take medication against my allergic symptoms on demand"; 3) "I don't take any medication against my allergic symptoms".

Additional questionnaires

In addition, we also assessed participants' expectations and hopes regarding the placebo treatment, the extent to which they felt informed about placebos, their actual knowledge about placebos, their self-efficacy beliefs, and their beliefs about a potential relationship between their allergic symptoms and COVID-19 (see supplement).

Statistical Analyses

After data screening, we performed an intention-to-treat analysis by estimating the missing values of the two persons who dropped out using the expectation maximization procedure according to methodological recommendations [31,32]. For the main analysis, we conducted two separate analyses of covariance (ANCOVA), with the severity and frequency of allergic symptoms at T2 as the dependent variable (DV), treatment (OLP vs. TAU) as a between-subjects factor, and baseline allergic symptoms (T1) as a covariate. For the secondary endpoint, we performed another ANCOVA with T2 impairment as the DV and T1 impairment as a covariate. Subsequently, we added medication use (no medication vs. regular medication vs. medication on demand) as an additional between-subjects factor to the aforementioned ANCOVAs. Type-1 error levels were set at 5%. All analyses were conducted using IBM SPSS Statistics Version 27.

Results

Primary Endpoint: Change in Allergic Symptoms

Symptom severity

The ANCOVA indicated no significant difference between OLP and TAU, although there was a non-significant trend pointing to somewhat more symptom improvement in the OLP group (adj. $M = 0.93$; $SE = 0.11$) than in the TAU group (adj. $M = 1.19$; $SE = 0.10$),F (1, 71) = 3.280, $p = .074$, $\eta^2_p = .044$. According to a sensitivity power analysis, the given sample size would have been sufficient to uncover a medium to large effect ($f = .330$) for this analysis, but the actually observed effect size for symptom severity was considerably lower ($f = .215$). Thus, the power was insufficient to unveil significant effects in this analysis. The reduction of symptoms in the two groups is depicted in Figure 3a and the corresponding descriptive values are presented in Table 2. Symptom severity at baseline was not significantly related to T2 severity,F (1, 71) = 3.368, $p = .071$, $\eta^2_p = .045$.

Insert Figure 3 here.

Symptom frequency

The ANCOVA indicated significantly greater symptom improvement in the OLP group (adj. $M = 1.89$; $SE = 0.11$) than in the TAU group (adj. $M = 2.29$; $SE = 0.10$), F (1, 71) = 7.272,$p = .009$, $\eta^2_p = .093$, as highlighted in Figure 3b and Table 2. This reflects a medium to large effect ($f = .320$). The effect of symptom frequency at baseline was also significant,F (1, 71) = 22.844, $p < .001$, $\eta^2_p = .243$. Differences between OLP and TAU in the frequency of specific symptom clusters are displayed in Figure 4 (and presented in detail in the supplement), suggesting that the effects of OLP as compared to TAU were particularly pronounced for eye-related symptoms, breathing-related symptoms, and general symptoms.

Insert Table 2 here.

Secondary Endpoint: Impairment caused by allergic symptoms

The ANCOVA indicated significantly more improvement in the OLP group (adj. $M = 1.39$; $SE = 0.16$) than in the TAU group (adj.$M = 1.93$; $SE = 0.15$), F (1, 71) = 6.445, $p = .013$, $\eta^2_p = .083$ (see Figure 3c and Table 2), reflecting a medium to large effect ($f = .301$). Impairment at baseline was also significantly related to impairment at T2, F (1, 71) = 14.689, $p < .001$, $\eta^2_p = .171$.

Insert Figure 4 here.

Effects of Medication Use

The treatment by medication use ANCOVA indicated that medication use had no significant effects on the reduction of symptom severity, F (2, 67) = 2.386, $p = .100$, $\eta^2_p = .066$, nor did it interact with the effects of treatment, F (2, 67) = 0.266,$p = .767$, $\eta^2_p = .008$. For symptom frequency, medication use also had no significant effects on symptom improvement, neither in terms of a main effect, F (2, 67) = 1.983, $p = .146$, $\eta^2_p = .056$, nor in interaction with the effects of treatment, F (2, 67) = 2.126, $p = .127$, $\eta^2_p = .060$. For the secondary outcome, there was a significant main effect of medication use on improvement of impairment, F (2, 67) = 4.189,$p = .019$, $\eta^2_p = .111$, with the least impairment at T2 in people who did not take any medication ($M = 1.02$;$SD = .82$) as compared to people who regularly took medication ($M = 2.04$; $SD = 1.32$) and people who took medication on demand ($M = 1.73$; $SD = .88$). The treatment by medication use interaction was not significant, F (2, 67) = 1.532, $p = .224$, $\eta^2_p = .044$.

Associations of symptom improvement with additional variables

In Table S1 in the supplement, we present the correlations of symptom burden with particpants' expectations regarding placebo treatment as well as the extent to which participants felt informed about placebos. The results indicate that expectations were not significantly associated with symptom burden after taking placebos (T2 or T3, respectively). The extent to which participants felt informed about placebos, however, was significantly associated with lower symptom frequency and lower symptom-related impairment in the OLP group.

Adherence and side effects

In the OLP group, 74% of the participants reported that they always took the placebos as prescribed, and 26% said they mostly did so. One participant in the OLP group reported abdominal pain as a side effect after taking the placebo. During the switch-over, one participant from the control group also reported that side effects had occurred during the first week of intake: The person reported gastrointestinal problems, problems falling asleep, itching of the skin and itching in the mouth as side effects.

Discussion

The present results show that although OLP did not significantly improve the severity of allergic symptoms in comparison to TAU, it did reduce the frequency of symptoms and the degree of allergy-related impairment. By distinguishing between symptom severity and symptom frequency, the current results can resolve the inconclusive findings from previous research on the effects of OLP in allergic rhinitis: Previous studies revealing a significant effect of OLP assessed symptom frequency only[21,22], whereas a previous study that failed to find a significant effect of OLP over TAU focused only on symptom severity[23]. Assessing both symptom severity and frequency, the present results suggest that OLP has medium to large effects on the frequency of allergic symptoms, whereas its effects on symptom severity are only small to medium (which failed to reach significance in the present study, possibly due to insufficient power to uncover such effects).

An altnernative interpretation of the discrepant results for the two symptom measures might be the breadth of symptoms being considered. More specifically, the symptom severity measure focuses on allergic symptoms related only to the nose and eyes, whereas the frequency questionnaire also considers additional symptoms. Indeed, the analysis of more specific symptom clusters suggests that the beneficial effects of OLP over TAU were particularly pronounced in symptoms pertaining to the eyes, breathing, and more general symptoms such as tiredness or trouble concentrating, whereas the majority of the items of the CSMS refers to nose-related symptoms. Thus, it might be that the CSMS is not ideal to capture the beneficial effects of OLP on the variety of allergic symptoms.

With regard to symptom-related impairment, it is worth noting that the present study, unlike previous studies [21-23], found that OLP significantly reduced impairment, with medium to large effects. Possibly, this is related to the fact that the present study, unlike previous work, used a questionnaire that assesses impairment specifically in the context of allergic symptoms. Thus, combining the present findings with prior research [21-23], it seems that OLP has the potential to reduce allergy-specific impairment, but not impairment more generally.

Given the positive results regarding the reduction of symptom frequency and impairment through OLP, the current findings suggest that a physical patient-provider interaction might not be necessary for OLP to work. This is an important finding with respect to the still ongoing COVID-19 pandemic and its restrictions of physical contact as well as increasing demand for online therapy. Taking the less positive results of a previous study administering OLP remotely into account[23], it may be important to make sure that patients can start taking the placebos immediately after the virtual encounter, as it was done in the present study. In line with that notion, participants from the TAU group who started taking placebos with a few days delay did not

show that much improvement as well. In addition, the correlational results suggest that it is important to ensure that patients are properly informed about the effects of OLP, since the extent to which participants felt informed about placebos was associated with lower symptom burden after taking OLP.

Limitations

The most significant limitation of the present study is its relatively low sample size. Althought the current sample size was larger than in all previous studies examining OLP in allergic rhinitis[21-23], it did not offer enough power to uncover small to medium effects, as it would have been necessary for the effects of OLP on symptom severity. Furthermore, the current study focused on self-reported allergic symptoms only, and future research may examine whether beneficial effects of OLP can also be observed on a physiological or immunological level.

Conclusions

The present results suggest that remotely provided OLP can improve the frequency of allergic symptoms as well as allergy-related impairment over TAU. OLP might also have beneficial effects on symptom severity, but this effect warrants further exploration using larger samples.

Acknowledgements

All authors developed the overall idea of the study. TK and AKB planned the specific operationalisation of the study. TK analysed the data and wrote the draft of the manuscript, supervised by IK and AKB. All co-authors reviewed the manuscript and provided critical feedback on it.

We are very grateful to Lea Balthasar and Valentina Riehl for their important work in the conduction of the study. In addition, we would like to thank the "Adler Apotheke", the local pharmacy in Landau, Germany, for their support in ordering the placebos used in the present study.

Conflict of Interest

The authors have no conflict of interest to declare. No funding was received for this study.

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Figure Legends

Figure 1. CONSORT diagram of participants' flow.

Figure 2. Procedure of the present study.

Figure 3. Effects of open-label placebo (OLP) vs. treatment as usual (TAU) on a) the severity of allergic symptoms, b) the frequency of allergic symptoms, and c) allergy-related impairment.

Figure 4. Effects of open-label placebo vs. treatment as usual on the frequency of different clusters of allergic symptoms.

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