General Practitioners Attitudes towards Open-Label Placebos in Australia.

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Abstract

Objective: Multiple studies have found between 18-70% of medical professionals prescribe placebos, with general practitioners' (GPs) reportedly being the highest prescribers. Even though placebos are common in clinical practice, patients and doctors alike have issues with the deceit involved, which is resolved with open-label placebos. The study looked at GPs attitudes towards traditional placebos and open-label placebos.

Method: Participants were practising GPs in Australia (N = 54). The study involved an online questionnaire composed of four different sections; demographics, attitudes towards traditional placebos and open-label placebos, understanding towards open-label placebo mechanisms and usage, and any concerns or comments they had towards open-label placebos.

Results: Differences found between traditional placebos and open-label placebos only involved GPs who were accepting of placebo interventions. GPs understanding of the underlying mechanisms being psychological and involving the patient/doctor relationship is in line with the current literature. The situational usage of open-label placebos in cases of non-specific or physical symptoms match with conditions commonly presented to GPs. The likelihood to prescribe open-label placebos did not appear to be influenced by demographic variables. The highest number of concerns and comments reported regarded patient acceptability and the lack of research in clinical practice.

Conclusion: This exploratory analysis has constructed an overview of general practitioners' attitudes towards placebos in Australia. Future research conducted with larger samples would be beneficial to evaluate demographic influences and the practicality of open-label placebos. This study indicated that open-label placebos are a viable treatment option in clinical practice pending further research.

Declaration

This thesis contains no material which has been accepted for the award of any other degree of diploma in any University, and, to the best of my knowledge, this thesis contains no material previously published except where due reference is made. I give permission for the digital version of this thesis to be made available on the web, via the University of Adelaide's digital thesis repository, the Library Search and through web search engines, unless permission has been granted by the School to restrict access for a period of time.

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Chapter 1: Introduction

1.1 Background

The World Health Organization (1948) defines health as "a state of complete physical, mental, and social well-being, and not merely the absence of disease or infirmity". When the health of a person is compromised, modern medicine often turns to treatment of a pharmacological nature, as it has become an integral part of medical practice (Fox, 2003). Whilst there are numerous benefits to this system, it does come at a financial cost to the patient, as well as the Australian Government (Fox, 2003). The Australian Government subsidises many commonly available drugs through the Pharmaceutical Benefits Scheme (Fox, 2003). This cost is growing and in 2016/17, it was to the tune of $12,058 million (Department of Health, 2017). Pharmacological treatment also has the risk of side effects (Howick et al, 2013). For example, the common best practice for treatment of chronic pain involves medications such as non-steroidal anti-inflammatory drugs (NSAIDs), which can have harmful side effects (Ward, Archambault & Mersfelder, 2010). Harmful side effects include stomach problems, kidney problems, high blood pressure, and heart problems (Turner & Connolly, 2018). Additionally, when medication, such as antibiotics, are taken frequently or incorrectly, there runs the risk of the emergence of bacterial antibiotic resistance (Ventola, 2015). Bacterial antibiotic resistance is becoming a significant problem due to the expensive, albeit lengthy, cost of treatment, and the creation of new medication (Ventola, 2015). As a result, other treatment options are being investigated as an alternative or adjunct to pharmacological treatment. One such treatment option, particularly those of a more holistic nature, lies in the realm of placebos and harnessing their effect as a way to lead to better health outcomes.

In this exploratory analysis, attitudes towards the use of placebos in clinical practice by general practitioners in Australia will be investigated. A summary of the research on the definition and mechanisms of placebos will be presented, followed by the current clinical use, attitudes and concerns towards them. The newly proposed open-label placebos (placebos without deception) will be introduced and the current literature regarding it will be reported. The overall aim is to examine general practitioners' attitudes towards open-label placebos, to begin building the picture of what is currently understood about them and offer direction for future research.

1.2 Definition of placebos

The definition of placebos in clinical practice is hard to define as it varies considerably in the literature (Colloca & Howick, 2018). For the purpose of this literature review, a commonly used definition of placebos is 'any intervention or treatment that objectively is known to have no specific effect, but for which a beneficial outcome occurs as a result of the patient believing in its efficacy' (De Deyn & D'Hooge, 1996). Part of the ambiguity around defining placebos is due to the 'placebo effect' and 'placebo response' often being lumped in the same category (Kirsch, 2013). A placebo response is an observable change following the administration of the placebo and typically utilised in clinical trials (Chaplin, 2006). On the other hand, a placebo effect is the change produced by the placebo treatment (Kirsch, 2013). It is the difference between the placebo response and no treatment (Howick et al., 2013).

The placebo effect varies depending on the condition or illness making it difficult to determine the overall effectiveness of placebos. Conditions reported as having the strongest placebo effects involve the pain reduction and insomnia (Kisaaltita, Staud, Hurley & Robinson, 2014; Yeung, Sharpe, Glozier, Hackett & Colagiuri, 2018). However, can also be found in

nausea, fibromyalgia, fatigue, and mood disorders have also been found (Chen et al., 2017; Cho, Hotopf & Wessely, 2005; Li, Li & Zheng, 2017; Quinn & Colagiuri, 2015). The placebo phenomenon also extends cross culturally. In African and South American cultures, healing rituals and herbal concoctions are commonly used when someone is ill, which are likened to placebo treatments in western medicine (Jara, 2014; Zimba & Buggie, 1993).

1.3 The mechanisms underlying the placebo effect

There are a few underlying mechanisms proposed to underlie the placebo effect. The most strongly researched mechanism is the classical conditioning paradigm (Colloca & Howick, 2018). It is believed that the act of taking a placebo treatment triggers a pharmacological memory and therefore acts as a conditioned cue for a previously learned response of getting/feeling better (Colloca & Howick, 2018). More recently, expectancy theory is being explored as a mechanism, due to a patient having a conscious expectation that the treatment will make them feel better (Colloca & Howick, 2018). Evidence of how it can mediate placebos and their outcomes is with cases of anxiety (Turner, Deyo, Loeser, Von Korff & Fordyce, 1994). If a patient takes a placebo with the expectation that they will feel better, it can lead to a reduction in anxiety and an increase in immune system functionality (Turner et al., 1994). In situations involving pain, the expectation of pain relief can modulate the central regulation of pain through different bodily symptoms, such as the dopamine reward system and the endogenous opioid system (Price, Finniss & Benedetti, 2008).

Emerging research suggests that the nature of the interaction between the practitioner and patient can also trigger the placebo effect (Jonas, 2011). The role practitioners play in administering medication is recognised as a key contributor to the health outcomes (Schaefer,

Sahin & Berstecher, 2018). This links back to expectancy theory where the expectation of a person feeling better can be enhanced by how effective a doctor's performance is (Czerniak, et al., 2016). A meta-analysis looking into the influence of context effects on health outcomes found overall that practitioners who adopted a warm, friendly and reassuring manner are more effective than those who conduct more formal consultations due to greater placebo responding and the role that expectations play (Di Blasi, Harkness, Ernst, Georgiou & Kleijnen, 2001). However, this effect appears to apply only to patients who are susceptible to placebos (also known as placebo responders); the practitioner's manner does not appear to affect people who are not susceptible to placebos (Czerniak et al., 2016).

1.4 The use of placebos in clinical practice

General practitioners (GPs) reportedly are the highest placebo prescribers (Hassan, Fauzi & Hasan, 2011). Underlying reasons offered surround the role that GPs play in health care. In Australia, general practitioners provide majority of medical primary health care, with 85% of Australians visiting their GP at least once a year (Gill, 2016). Furthermore, there is a wide range of medical conditions that general practitioners see compared to their specialist counterparts (Gill, 2016). Estimates put almost half of all GP consultations as not being possible to make a diagnosis that fits with the typical diagnostic criteria, due to the fleeting nature of symptoms (Gill, 2016).

In a systematic review looking into placebo usage by general practitioners in clinical practice, twenty-two cross-sectional studies from twelve countries were analysed (Fassler, Meissner, Schneider & Linde, 2010). The review found placebo usage in clinical practice is not negligible, and that impure placebos are used more than pure placebos (Fassler et al., 2010). In

summary, impure placebos (also referred to as 'active' placebos) have pharmacological effects, however the effect on the disease at hand has not been proven, and is uncertain (Bishop, Aizlewood & Adams, 2014). This includes nutritional supplements advised or prescribed for patients who are not nutritionally deficient, or antibiotics prescribed for patients who have viral infections (Bishop et al., 2014). Pure placebos (also referred to as 'inactive placebos') have no pharmacological effects, two such examples being saline injections and sugar pills (Bishop et al., 2014).

In Germany, 45% of GPs surveyed used pure placebos compared to 76% who used impure placebos (Meissner, Hofner, Fassler & Linde, 2012). A similar study in the United Kingdom of 782 GPs found that 97% had used either kind of placebo at least once in their career, with as many as 77% of practitioners having used some sort of impure placebo at least once a week (Howick et al., 2013). The study also found gender effects; females were more likely to use placebos via positive suggestions and non-essential physical exams (Howick et al., 2013). An explanation offered was the number of days per week doctors spent in practice and number of patients they saw per week (Howick et al., 2013). They found in the sample that 92% of GPs working 0-3 days used non-essential physical exams frequently compared to 77% of participants who worked 5 days or more (Howick et al., 2013). As female doctors typically worked less days, hence seeing less patients, which may explain why they were more likely to use non-essential physical exams (Howick et al., 2013).

The age of the general practitioner has also found to influence the frequency of placebo distribution. Younger GPs were significantly more likely to prescribe placebos compared to their older counterparts (Braga-Simoes, Soares Costa & Yaphe, 2015). However, these effects have not been replicated by other studies (Meissner et al., 2012). A study looking at orthopaedic

surgeons' placebo usage found that years in practice influenced how likely they were to prescribe placebos (Baldwin, Wartolowska, & Carr, 2016). Trainee surgeons were more likely to prescribe placebos compared to more senior surgeons (Baldwin et al., 2016). However, it is unclear whether the likelihood to utilise placebo interventions is impacted by age, years of experience, or a mixture of both. As of yet, placebo usage by Australian GPs has not been researched.

1.5 Attitudes towards placebos in clinical practice

The clinical situation influences the likelihood of placebos being prescribed. Circumstances, in which placebos have reported being administered, include anxiety, pain, agitation, vertigo, sleep problems, asthma and withdrawal from recreational drugs (Nitzan & Lichtenberg, 2004). It is the general consensus amongst medical practitioners that in situations where there is a severe infection, fractures, cancers or any other biological failure, placebos shouldn't be offered as a treatment option (Olesen, 2015). Rather, situations where placebos may be beneficial surround the alleviation of symptoms (Olesen, 2015). This is due to the nature of symptoms being quite complex and influenced by many factors such as cultural, social, and personal influences (Winkelman, 2010). In particular, social factors are able to modulate physiological and biological responses and alongside psychological processes, can influence multiple biological systems and affect the progression of a disease (Ader, 2007). The symptoms of the disease can be manifested into anxiousness, depression, dizziness, pain, nausea, and tiredness to name a few (Olesen, 2015). It is often believed by the medical literature that the placebo response differs according to the nature of the illness with most placebo responses being attributed to psychosomatic symptoms (Fent, Rosemann, Fassler, Senn & Huber, 2011). Moreover, they found that most GPs thought that placebos were ethically acceptable in certain

circumstances and would tell their patients that the intervention had helped other patients without specifically telling them it was a placebo (Howick et al, 2013). This is where the ethical lines become blurred and is often the course of many debates (Howick et al., 2013).

Previously, it was a common thought amongst academics and practitioners that the main purpose of placebos was to distinguish between whether a patient's symptoms were "real" or "fake" (Goodwin, Goodwin & Vogel, 1979). It is only quite recently that a growing number of practitioners report recognising that placebos might have therapeutic effects (Sherman & Hickner, 2008). In a study looking into the situational use of placebos, the authors found that practitioners used placebos as a supplement to main therapy (61%), a diagnostic tool (32%), to calm a patient (33%), to satisfy/ mollify a patient (23%), to control pain (23%) and instead of using medicine when using medicine is not justified (9%; Shah, Panchal, Vyas & Patel, 2009). The perceived mechanism of action has been described by practitioners as being mainly due to psychological mechanisms, however a combination of psychological and biochemical effects has been suggested, to a lesser degree (Nitzan & Lichtenberg, 2004). This is supported by other studies conducted with orthopaedic surgeons, where most believe that the placebo effect is due to psychological mechanisms, with a smaller number believing it is because of conditioning, natural history of disease and unexplained factors (Baldwin et al., 2016; Wartolowska, Beard & Carr, 2014).

Whilst there appears to be a role for placebos in healthcare due to the beneficial health outcomes associated with them, there are concerns as well. One concern regards the negative health outcomes, also known as 'nocebo effects' (Colloca, 2017). Nocebo effects are adverse events produced by negative expectations, compared to the positive expectations that trigger placebo effects (Colloca, 2017). Like the placebo effect, multiple factors such as the

psychosocial context and therapeutic environment on a patient's mind, brain and body (for example negative information and prior unsuccessful therapies) can produce them (Colloca & Finniss, 2012). Doctors have reported concern with potential legal problems that could arise following the use of placebo interventions, if there were negative health outcomes (Baldwin et al., 2016; Wartolowska et al., 2014).

Other concerns raised center around ethical use. One ethical issue is the endangerment of the doctor-patient relationship (Kisaalita, Roditi and Robinson, 2011). This is acknowledged across multiple studies where doctors have continually mentioned the risk of deterioration of the doctor-patient relationship (Baldwin et al., 2016; Wartolowska et al., 2014). In the study undertaken in the United Kingdom, they found that 90% of GPs agreed that placebos involving deception were unethical when they endangered the patient/doctor relationship (Howick et al., 2013). When patient's perspectives on placebo administration has been studied, it has been found that doctor approval is highly dependent on the deceptiveness of placebo administration (Kisaalita et al., 2011). To put quite simply, if a patient wants an effective treatment (commonly expecting a pharmacological treatment) yet receives a placebo instead, this can be seen as an unethical, violation of the patient's right to be honestly and fully informed about treatment (Lichtenberg, Heresco-Levy & Nitzan, 2004). The study undertaken in the UK found majority of GPs stated that placebo interventions were unacceptable when they involved deception (Howick et al., 2013).

1.6 Open-label placebos

Open-label placebos have been offered as a way to mitigate some of the ethical and practicality issues that are currently found with traditional placebos, as they challenge the

widespread belief that placebos require deception in order to be effective (Kapthuck et al., 2010). The idea behind open-label placebos is patients are explicitly made aware they have been given a placebo hence eliminating the deception aspect (Carvalho et al, 2016). Early research shows disclosing to the patient that they are receiving a placebo does not necessarily diminish its effectiveness (Kisaalita et al., 2011). Moreover, having contextualised informed consent can reduce nocebo responses as it allows doctors to tailor the information about the possible treatment side effects to the patient (Wells & Kaptchuk, 2012). A study examining placebo interventions in practice from both the patients and practitioner's perspective found that most patients were in support of placebo treatments, with 70% wanting to be informed that they were to be given a placebo (Fassler, Gnadinger, Rosemann & Biller-Andorno, 2011). This lends support from a patient's perspective of open-label placebos.

1.7 Clinical Trials into Open-Label Placebos

While the practical use of open-label placebos is currently under-researched, the first experiment looking into placebos without deception can be backdated to 1965. In the 1965 experiment, Park and Covi set out with the 'paradoxical' experiment by giving participants who suffered with anxiety, pills with no active medication in them. Although there was a low number of participants due to the nature of the trial, they found that patients had significant symptom improvement as well as the treatment rating highly by both the patients and practitioners (Park & Covi, 1965).

It is only just recently that the idea of open-label placebos has come back into the literature, when Kaptchuck and colleagues undertook a small-randomized controlled trial. Their study included 80 Irritable Bowel Syndrome (IBS) sufferers who were given either open-label

placebo pills or no treatment controls (Kapthuck et al., 2010). They found there was a significant improvement in the group given the placebo compared to the group that had no treatment (Kapthuck et al., 2010). The main aim of their study was to challenge the notion that therapeutic use of placebos requires deceit and to remove the ethical conundrum that practitioners potentially face (Kapthuck et al., 2010). They were able to demonstrate that placebo effects can be harnessed without deception, thus coined the term 'open-label placebo'.

Further studies have aimed to replicate this effect in varying conditions and diseases. One such condition is chronic pain. Carvalho and colleagues (2016) tested 83 participants with ongoing chronic lower back pain. Participants were randomized into two groups; one who would receive the open-label placebo and the other group who would continue their current treatment (Carvalho et al., 2016). After 21 days, they found that open-label placebos had a statistically significant benefit over the treatment as usual group (Carvalho et al., 2016).

More recently, open-label placebos have been suggested as a treatment option for cancer-related fatigue. Traditionally, pharmacological treatments for cancer-related fatigue are only marginally effective or are not statistically significant compared to placebos, however still have sizeable side effects (Hoenemeyer, Kapthuck, Maheta & Fontaine, 2018). In a study comparing open-label placebos to 'treatment as usual' controls, it was found that open-label placebos corresponded with a significant improvement of roughly 29% on average in fatigue severity and a 39% improvement with fatigue-disruption on quality of life compared to the treatment as usual group (Hoenemeyer et al., 2018). Open-label placebos also had no reported adverse events or side effects (Hoenemeyer et al., 2018).

The comparison between traditional placebos and open-label placebos has also been researched. In a study comparing the two analgesic placebos, they found that there was a

significant improvement between the two placebo groups and the control group, whereas there was not a significant difference between the two placebo groups (Mundt, Roditi & Robinson, 2017). This lends support to the idea that placebos do not require deception in order to be effective.

1.8 Current study

Whilst there is emerging research surrounding the benefits of open-label placebos in the general population, the GPs' role is still heavily under-researched. This study will build on current literature by looking at GPs' perspectives, based on the fact that they are the most likely group to prescribe placebos compared to any other medical disciplines (Hassan et al., 2011). Therefore, the overall aim of this study is to investigate GPs' attitudes towards open-label placebos in Australia. This will be firstly be addressed with the following research questions:

1) Do general practitioners' attitudes towards traditional placebos differ from their attitudes towards open-label placebos, and
2) What are general practitioners' attitudes regarding open-label placebo mechanisms and usage?

Following on from the conclusions revealing gender differences in willingness to provide placebos in Howick's (2013) study, it is hypothesised that:

1) Women will be more willing to prescribe open-label placebos, compared to males,
2) General practitioners seeing less patients per week will be more willing to prescribe an open-label placebo compared to those who see more patients per week, and

3) The gender difference in the likelihood to prescribe open-label placebos will be due to the number of patients seen per week.

Moreover, in line with the past research conducted by Braga-Simoes (2015) and in other medical disciplines (Baldwin, et al., 2016; Wartolowska, et al., 2014), it is hypothesised that:

4) Younger general practitioners will be more likely to prescribe open-label placebos compared to their older counterparts,
5) General practitioners who have spent less years in practice will be more likely to prescribe open-label placebos, and
6) This age difference in the likelihood to prescribe open-label placebos is due to the number of years in practice.

Lastly, in order to inform future research, a last research question will address whether general practitioners' have any concerns and additional comments regarding open-label placebos.

Chapter 2 Method

2.1 Participants

The study consisted of General Practitioners in Australia (N= 54) with females (n = 35) and males (n = 19), aged 25 years or older. Participants were accrued between April and July 2018 through two posts in the closed Facebook group 'GPs Down Under' (see reference for website URL) on the 17th of May 2018 and 23rd of June 2018. At the time, there were 5,604 members in the group. Emails were also sent out via the Northern Health Network (formally known as Sonder as of July 2018; see reference for website URL), Home Doctor's July newsletter (see reference for website URL), Australasian Association for Academic Primary Care (AAAPC), and randomly selected general practices in South Australia. Participants were

required to be fluent in English and to be active in general practice in Australia. Participation was voluntary and no incentive for participation was provided.

2.2 Measures

Participants were required to complete an on-line questionnaire for the study. The questionnaire was designed specifically for this study based on previously published surveys (Babel, 2013 Howick et al., 2013; Wartolowska et al., 2013) and was comprised of three different sections.

The first part of the questionnaire collected participant demographics, including their age, gender, years practising, average number of patients seen per week, where they completed their basic medical degree, and their perceived culture.

The second part of the questionnaire was designed to gather attitudes towards traditional placebos. As there has been some confusion surrounding what constitutes a placebo, the definition given was that a placebo is "any intervention or treatment, that objectively is known to have no specific effect, but for which a beneficial outcome occurs as a result of the patient believing in its efficacy" (Baldwin et al., 2016). The reason why the broad definition of a placebo was used, as opposed to breaking it down into pure and impure placebos like some other studies, was to keep it simplified, as the main focus of the study was to look at the attitudes towards open-label placebos. This definition also has had a high agreeance rate in the previous studies it has been used in (Baldwin et al., 2016; Hrobjartsson & Norup, 2003; Wartolowska, et al., 2013). Participants were then asked whether they agreed with the definition and to provide any additional comments they have.

Ten items were used to collect attitudes towards traditional placebos. The first two questions asked about their beliefs on the effectiveness of placebos and whether they can produce physical changes in the body, answered by a yes/no/don't know response. The next four questions evaluated ethical attitudes, place in clinical practice, and likelihood to prescribe traditional placebos. The first three questions were rated on the same 5-point scale (strongly agree, agree, neither agree or disagree, disagree, and strongly disagree). The last question was rated on a different 5-point scale (highly likely, likely, unlikely, highly unlikely, and don't know). The next two questions asked what the underlying mechanism/s and situational circumstances where participants were able to choose from a pre-set selection of answers (Baldwin et al., 2016). The last question was open-ended and asked what their concerns were with traditional placebos.

The third part of the questionnaire introduced open-label placebos. Following a similar format to the second part of the questionnaire, participants were given a definition of an open-label placebo; "Recent studies have shown that placebos can produce beneficial effects even when patients are told that they are receiving placebos. In other words, deception is not needed to achieve a therapeutic placebo response. This is referred to as an 'open-label' placebo". Eight items were then used to gather attitudes towards open-label placebos. The first two questions asked was whether they think it can be effective and whether it can produce physical changes in the body. Like above, they had the option to respond yes/no/don't know. The next three questions asked were ethics, place in clinical practice and likelihood to prescribe where they could answer on a 5-point scale in the first two questions (strongly agree, agree, neither agree or disagree, disagree, and strongly disagree), and the third (highly likely, likely, unlikely, highly unlikely, and don't know). Participants were then asked what they thought the underlying mechanism/s is/are, broad situations where they would consider using, and groups of illness/conditions they would

consider using open-label placebos in. They could select from a pre-set range of responses and/or add their own additional comment. Participants were also asked to provide any additional concerns surrounding open-label placebos.

2.3 Procedure

Participants were invited to participate in the survey by accessing the survey website link via survey monkey. Prior to commencing the questionnaire, participants read the participation information sheet (Appendix 1) and provided inform consent (Appendix 2). Responses were entered directly into the online survey. Participants completed the online survey without any time constraints. The participants were advised that the survey would take between 15-20 minutes; however the average time taken was 7 minutes. Participants were given an option at the end to provide an email address if they wished to receive a summary of results.

2.4 Ethical Considerations

This study received approval from the University of Adelaide's Human Research Ethics Committee. Confidentiality of participants were ensured to allow them to answer the questionnaire as honestly as possible. No participant names were linked with any of the completed questionnaires and participants were allowed to withdraw from the study at any point.

2.5 Statistical Analyses

Data was analysed using IBM SPSS Statistics, Version 22. Demographic data and comparative data for deceptive and open-label placebos was summarised using percentages to describe the responses to each question. When participants were allowed to choose more than

one answer to a particular question, the percentages did not add up to 100 and were therefore excluded. Two-way Analysis of Variances (ANOVA) with Tukey HSD post-hoc tests were used to explore the interaction of variables affecting the likelihood to prescribe open-label placebo treatment.

Assumptions checked include searching for outliers on a scatterplot, using a histogram to make sure the outcome variable was normally distributed, and searching for missing data. Levene's test for homogeneity of variance was used for the two-way ANOVAs. A p-value $\leq .05$ was considered significant. Effect sizes are reported alongside exact p-values. The cut-off scores for the effect sizes for Cohen's d *(d)* are represented as 0.20 for small, 0.50 for moderate, and 0.80 for large effects (Cohen, 1988).

Chapter 3: Results

3.1 Sample characteristics

The sample characteristics can be found in Table 1. There were 54 participants who took part in the survey, with 41 complete responses (76% completion rate). The participants were mostly female, completed their basic medical degree in Australia, identified with Western culture, and saw between 51-100 patients per week. There appeared to be an even spread of ages, with the majority of Participants having been in practice for less than 10 years.

Table 1

Sample characteristics of participants (N = 54)

Category	Count (%)
Gender	
Female	35 (65)
Male	19 (35)
Age	
25-39	19 (35)
40-54	21 (39)
55+	14 (26)
Years Practising	
Less than 10 years	23 (43)
10-19	12 (12)
20-29	10 (18)
30-40	7 (13)
More than 40 years	2 (4)
Patients a week	
Less than 25	10 (19)
25-50	11 (20)
51-100	22 (41)
More than 100	11 (20)

3.2 Definition of placebo and placebo usage

The majority of participants (n = 45, 88%) agreed with the provided definition of placebo. Six Participants disagreed with the definition of placebos and offered additional comments, such as: the patient did not necessarily have to believe in it (n = 3), the doctor's role needs to be included (n = 1), and placebo effects are objective and measurable (n = 1). One participant believed that every treatment (including those of a pharmacological nature) has a degree of placebo response, so the definition was incomplete (n = 1). The frequency that Participants have prescribed or suggested a traditional placebo can be found in Table 2.

Table 2

Previous placebo usage (N = 51)

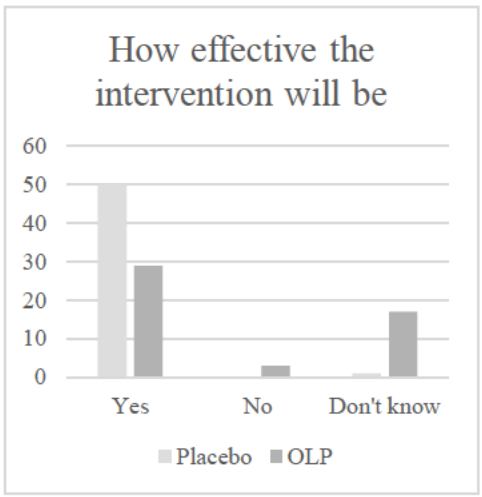
Previous placebo prescription/ suggestion	Count (%)
Never	17 (33)
Rarely (<1 per year)	12 (24)
Occasionally (>1 per year)	13 (25)
Often (>1 per month)	4 (8)
Frequently (<1 per week)	5 (10)

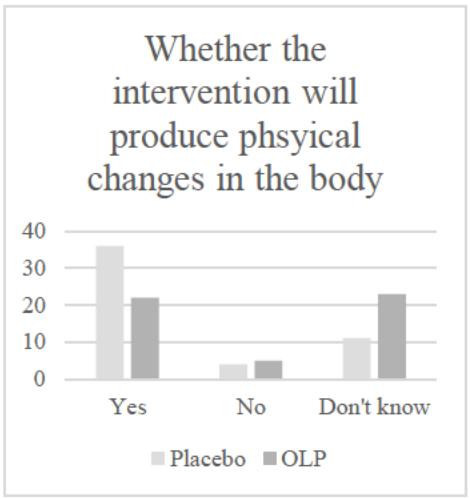
3.3 Do General Practitioners' attitudes towards traditional placebos differ from their attitudes towards open-label placebos?

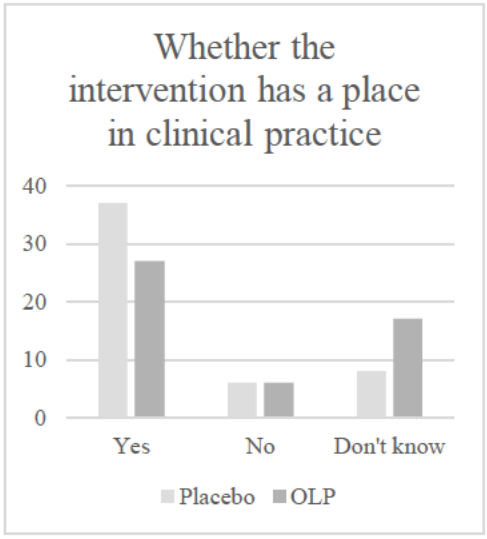
Participants were asked to answer identical statements surrounding their beliefs towards traditional placebos and then again with open label placebos as shown in Figure 1. All but one participant believed that traditional placebos can be effective (n = 50, 98%) with most believing they can produce physical changes in the body (n=36, 72%). This is compared to around half of participants believing open-label placebos can be effective (n = 29, 55%) and can produce physical changes in the body (n = 22, 45%). Whilst 'yes' responses varied depending on the question, 'no' responses remained fairly equal across both placebo interventions and the questions. For open-label placebos, where 'yes' responses decreased, 'I don't know' responses increased. Most participants believed that traditional placebos have a place in clinical practice (n = 37, 73%) whereas half believed the same with open label placebos (n = 27, 54%). Roughly the same number of participants would prescribe both traditional placebos (n = 28, 55%) and open-label placebos to an adult (n = 26, 52%). Just over half of participants believed that traditional placebos can be delivered ethically (n = 31, 61%) compared to open-label placebos (n = 37, 74%).

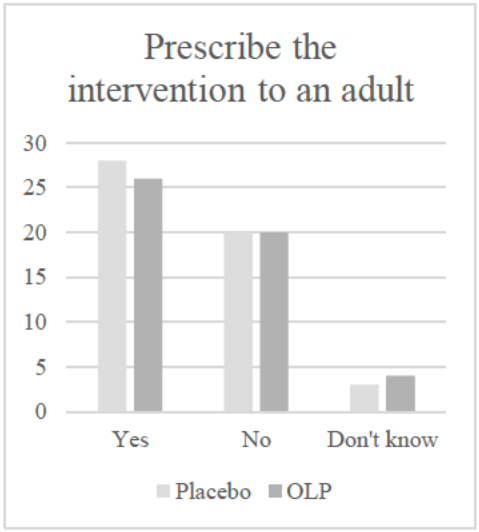
Attitudes towards traditional placebos and open-label placebos.

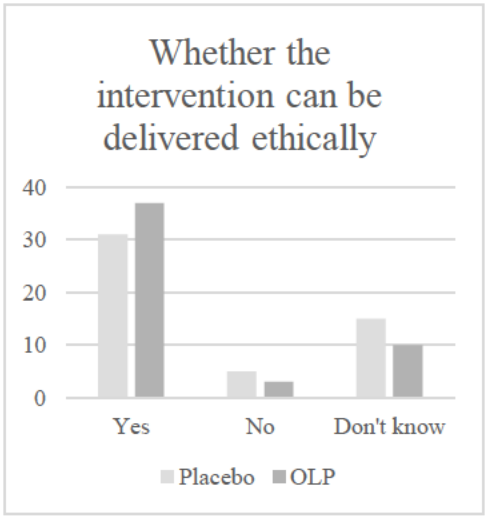
Figure 1











3.4 Attitudes regarding open-label placebo mechanisms and usage

For attitudes regarding open-label placebo mechanism and situational use, percentages were not provided, as participants were allowed to select more than one response (refer to Table 3). The majority of participants reported that the mechanism behind the open-label placebo effect are because of psychological reasons such as expectations, the patient/doctor relationship, or the natural course of the disease. In relation to situational context, majority of participants believed it to be a suitable treatment for non-specific symptoms, to control pain, and when all other therapies have been exhausted. The groups of illness/diseases that the participants indicated they would consider using an open-label placebo was mainly for sleep issues, physical symptoms such as pain, itchiness and excessive sweating and mood disorders such as anxiety, depression and panic attacks.

Participants were also given the opportunity to add any additional comments. The six comments given were in relation to using open-label placebos for psychological disorders, somatisation, fixed issues, self-limiting diseases, and any complex problem for which trial and review of treatment is an appropriate course guided by the patient's values and beliefs. Two participants said there were no situations in which they would consider using an open-label placebo, or would only consider it if there were clear evidence supporting its use in specific cases.

Table 3

Attitudes regarding the mechanisms and situations with open-label placebos

Question	N	Count
In your opinion, what is the mechanism behind the open-label placebo effect?	47	
Psychological/Expectations		38
Patient/doctor relationship		37
The natural course of the illness		32
Conditioning		15
Physiological		12
Positive energies		1
Unexplained factors		19
Other		4
Would you ever consider the use of an open-label placebo in these situations?	41	
As a diagnostic tool		11
When all other therapies have been exhausted		23
As a treatment for a non-specific symptom		33
To calm or mollify a complaining patient		18
To control pain		25

Would you ever consider the use of an open-label placebo for these groups of illnesses/disease?	42
Physical illnesses (i.e. hypertension, cancer etc.)	8
Physical symptoms (i.e. pain, itchiness and excessive sweating etc.)	33
Mood disorders (i.e. anxiety, depression, panic attacks etc.)	28
Sleep issues	37
Other	11

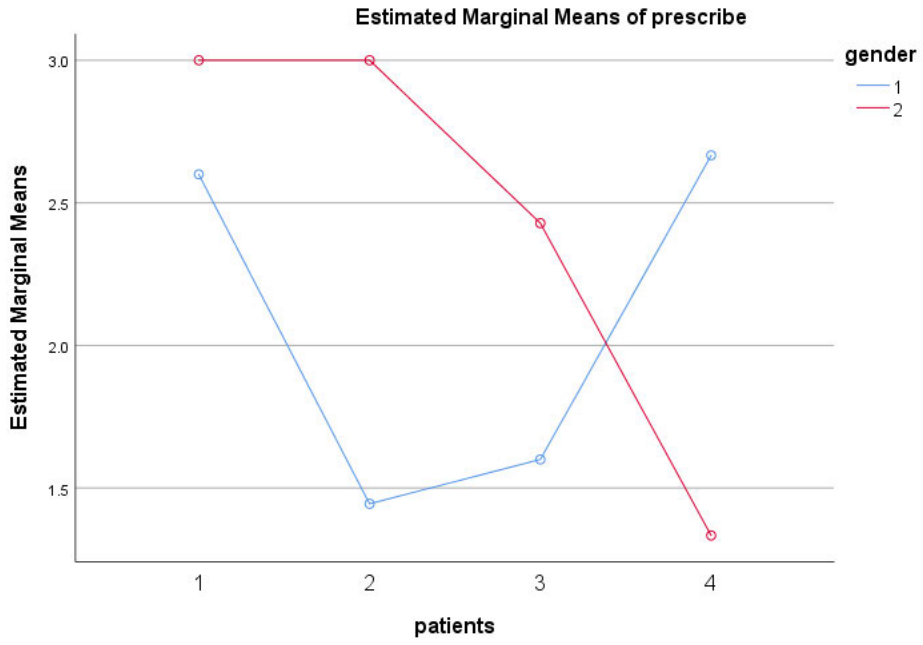
3.5 The influence of demographic variables on the likelihood to prescribe open-label placebos

The first three hypotheses predicted that women will be more likely to prescribe open-label placebos compared to males due to seeing less patients per week. Participants were divided into 2 groups according to their gender (Group 1: Female; Group 2: Male). Participants were also divided into four groups according to the number of patients seen per week (Group 1: less than 25; Group 2: 25-50; Group 3: 51-100; Group 4: more than 100). The results from a two-way ANOVA showed the interaction effect between gender and patients seen per week was not statistically significant, $F(3,42) = 1.60$, $p = .20$ and had a small effect size (partial eta squared = .10). The main effect for gender showed that females were more likey to prescribe an open-label placebo than males but this did not reach statistical significance, $F(1,42) = 0.55$, $p = .46$ and had a small effect size (partial eta squared = .01). The main effect for patients seen per week

was also not statistically significant, $F(3,42) = 0.83$, $p = .47$ and had a small effect size (partial eta squared = .06).

Effects of gender on likelihood to prescribe placebos due to number of patients seen per week

Figure 2

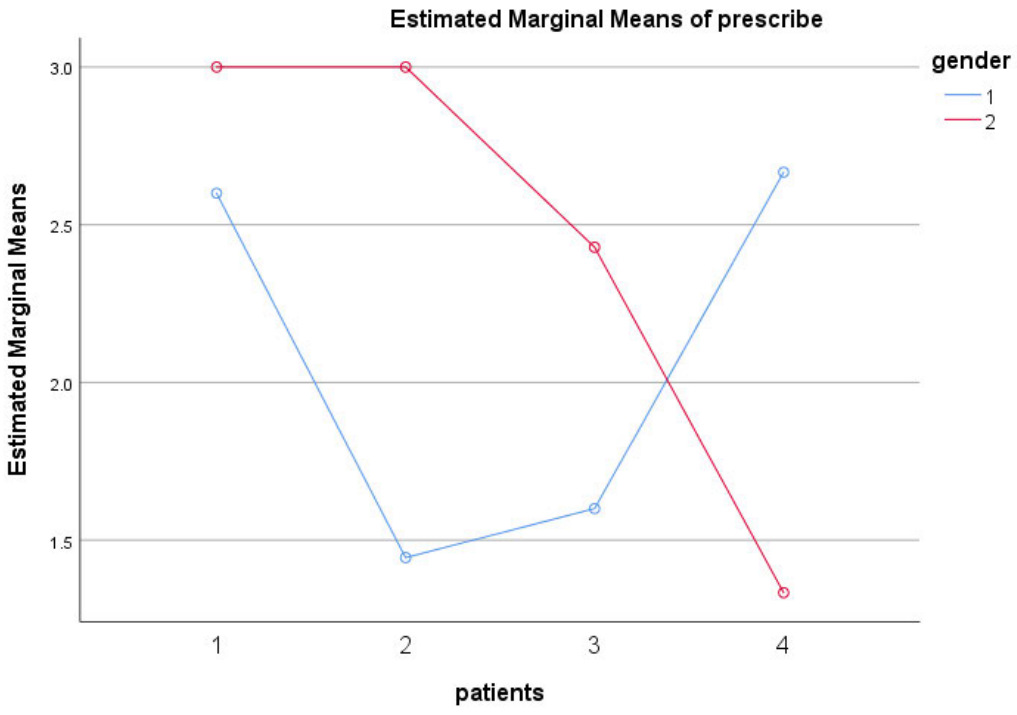


The last three hypotheses predicted that younger practitioners will be more likely to prescribe open-label placebos compared to males due to spending less years in practice. Participants were divided into three groups depending on their age (Group 1: 25-39; Group 2: 40-54; Group 3: 55+). Participants were also divided into five groups depending on how many years they have been practising (Group 1: less than 10; Group 2: 10-19; Group 3: 20-29; Group 4: 30-40; Group 5: more than 40). The results from a two-way ANOVA showed the interaction effect between age and years practicing was not statistically significant, $F(2,41) = 1.39$, $p = .26$

and there was a small effect size (partial eta squared = .06). There was a statistical significant result for years practising, $F(4,41) = 2.95$, $p = .03$; however the effect size was small (partial eta squared = .22. Further post-hoc comparisons using the Tukey HSD indicated that the mean score of the different groups was not statistically significant. The main effect for age was not statistically significant, $F(2,41) = 0.02$, $p = .98$ and there was no effect size (partial eta squared = .01).

Effects of gender on likelihood to prescribe placebos due to number of patients seen per week

Figure 3



3.6 General practitioners' concerns and comments regarding open-label placebos.

Throughout the survey, thirty-three participants left comments regarding additional comments or concerns regarding open-label placebos. Most additional concerns regarding open-label placebos centred on the patient's perspective (n = 10). These comments ranged from patient acceptability (n = 3) informed consent (n = 3), patients' expectations (n = 1) and patients misunderstanding of what an open-label placebo (n = 1). Two participants believed that the only way placebos work is if the patient still believes that it is efficacious and not "inert", hence a traditional placebo. Secondly, concerns around the lack of efficacy and research in clinical practice were raised (n = 6), with one participant believing they have a lack of experience in this area (n = 1). They went on to say they were worried it may get in the way of "proper" investigation and treatment, which was echoed by another participant (n = 1). Moreover, it was commented that open-label placebos should be used only when delay in successful treatment would not be a problem (n = 2). Furthermore, participants (n = 2) believed that the open-label placebo still requires deception and one participant worried about potential litigation if it does not work.

There were a few positive comments made by participants towards open-label placebos (n = 7). These include embracing open-label placebos due to reasons such as the benefits only marginally outweighing the risks for some pharmacological medications (n = 1), realisation that they use placebo therapy already in other forms (n = 2), and there are certain situations, such as those on opiates and benzodiazapam, that they believe open-label placebos could be beneficial for (n = 1).

Chapter 4: Discussion

4.1 Overview of study

The purpose of this study was to investigate general practitioners' attitudes towards open-label placebos. More specifically, this study aimed to explore attitudes between traditional and open-label placebos, perceived underlying mechanisms, situational usage, demographic influences on the likelihood to prescribe, and additional concerns and comments with open-label placebos.

4.2 Definition and frequency of use of placebo interventions in clinical practice

In the present study, 88% of participants agreed with the definition of placebo provided. This result is consistent with other studies using the same, or similar, definition of placebo (Baldwin, et al., 2016; Babel, 2013; Hrobjartsson & Norup, 2003). One participant who disagreed with the definition stated that the patient and treating doctor needed to be included in the definition. This foreshadows the belief that a strong underlying mechanism is the patient/doctor relationship.

Sixty-seven percent of general practitioners surveyed had prescribed or suggested a placebo intervention in their career. This result is lower than reported in other countries such as the United Kingdom (97%), Germany (88%), Denmark (86%), and Poland (80%) (Babel, 2013; Howick et al., 2013; Hrobjartsson & Norup, 2003; Meissner et al., 2012). However, this is higher than reported in the United States (56%; Kermen et al., 2010). A reason for this difference could be the geographical location and subsequent health care systems, medical education and culture. Another difference is United States does not have 'General Practitioners', rather 'Primary Care Physicians' (National Center for Health Statistics, 2018). These two terms are not synonymous,

therefore indicating the different roles they play, which may account for some of the difference in results (National Center for Health Statistics, 2018). Moreover, differences could have resulted from the wording of questions between the studies. In the United Kingdom, placebo interventions were separated into pure and impure placebos, with specific examples given, such as positive suggestions, non-essential physical exams and sugar pills (Howick et al., 2013). The study undertaken in Poland did not refer to placebos explicitly, rather identified them as non-specific methods (Babel, 2013). Perhaps if the current research followed the same format of either of these studies, results reported of placebo prescription may have been higher. In addition, the present study examined placebo prescription over shorter periods (e.g. at least once a week, once a month, once a year etc.) whereas the Danish and United States studies conducted longer periods of examination/observation (e.g. how many times per year do you placebo placebos?) (Hrobjartsson & Norup, 2003; Kermen et al., 2010).

4.3 Research Question 1: Differences between Traditional and Open-Label Placebos

The first research question intended to examine whether general practitioners' attitudes towards traditional placebos and open-label placebos differed. This was included because there does not appear to be any research on Australian GPs' attitudes towards placebo interventions. Asking questions surrounding traditional placebos allowed a solid comparative basis for attitudes towards open-label placebos, with an aim to pinpoint any differences. A major/ pattern within the results was that 'no' responses by participants appeared to be evenly spread between traditional placebos and open-label placebos. This indicated that participants were against placebo interventions collectively and the open-label aspect did not affect their feelings. Participants' reasons given in subsequent comments included interventions involving deception and their

disbelief that placebo interventions work. The number of 'no' responses were low for the first three questions regarding the placebo effect and clinical practice ($n \geq 6$), however, responses quadrupled for whether they would prescribe the intervention to an adult ($n = 20$). This shows they are rather accepting of the placebo in clinical practice, although are hesitant to use it themselves. Reasons for this are discussed below.

Another major finding was that the number of 'don't know' responses increased with open-label placebos. This highlights that GPs are not against open-label placebos, although indicates that they are unsure of the practicality. This is reflective of the limited research conducted in the area (Charlesworth et al., 2017). Lastly, the number of 'yes' responses from traditional placebos to open-label placebos decreased, particularly for the first three questions. This represents the shift to 'don't know' responses, and the gap in the literature.

The last question regarding whether the intervention can be delivered ethically was the only question where answers for open-label placebos did not follow the above trends. As such, 'yes' responses were higher, and 'no' and 'don't know' responses were lower. This is significant as one of the biggest concerns previously raised around placebo interventions were the ethical implications, in particular traditional placebos involving deception (Kisaalita et al., 2011). By removing the deceptive aspect, 72% of participants believed placebos can be delivered ethically (up from 60%), and only a small number believing they cannot (6%). This result highlights that open-label placebos are a viable treatment option pending further research, due to the decreased ethical implications that has occurred due to the removal of deceit.

4.4 Research Question 2: Underlying mechanisms and usage

The second research question evaluated the perceived mechanisms and situational usage of open-label placebos. The majority of GPs surveyed believed the underlying mechanisms are (1) psychological reasons/expectations, (2) the patient/doctor relationship, and/or (3) the natural course of disease. The first mechanism, psychological reasons/expectations, aligns with past findings from studies conducted in Poland, Denmark, and the United States (Babel, 2013; Hrobjartsson & Norup, 2003; Kermen, et al., 2010). Therefore, it echoes the emergence of Expectancy Theory being part of the explanation behind placebos (Colloca & Howick, 2018). The mechanism of the patient/doctor relationship was a close second among GPs. This shows that GPs are aware of how their interaction with a patient in consultations can elicit certain health outcomes (Schaefer, et al., 2018). Therefore, GPs should be involved in the creation of strategies to implement open-label placebos in clinical practice, in a manner that avoids deception and maximises health outcomes. The third proposed mechanism, natural course of the illness, provides insight into the nature of general practice and circumstances involving placebo interventions. GP's often address a range of fleeting symptoms, thus placebo efficacy increases as patients' symptoms are alleviated over the natural course of the illness. However, they attribute this to the prescribed placebo by prescribing placebo interventions, resulting in a belief by the patient that it has 'worked' (Gill, 2016). For example, prescribing antibiotics to a patient that has a cold (Kenealy & Arroll, 2013). The patient will likely recover on his or her own due to the natural course of illness, rather than the effects of the antibiotics (Kenealy & Arroll, 2013). However, when antibiotics are taken, there is the risk of side effects and antibiotic resistance bacteria (Kenealy & Arroll, 2013). Potentially, GP's could instead prescribe open-label placebos,

which would trigger the placebo effect with the benefit of decreasing the side effects, associated with pharmacological treatment.

Furthermore, common situational contexts that participants would use open-label placebos are for (1) non-specific symptoms, (2) when all other therapies have been exhausted, and (3) to control pain. This contradicts Goodwin's (1979) study that argued the majority of doctors used placebos to determine whether patients were exhibiting real or exaggerated symptoms. This reflects the shift in views of modern medicine towards support for the mind-body connection (Sherman & Hickener, 2008). Due to the nature of general practice, the first preference of non-specific symptoms were to be expected (Gill, 2016). Secondly, GPs utilising placebo treatments when all other therapies have been exhausted could be due to the trial and error process that GPs endure in the treatment of conditions and symptoms (Le Roux, Powell, Banks & Ridd, 2018). Respondents' third selection, controlling pain, is no surprise considering it is one of the most common areas researched relating to the placebo effect, and has demonstrated extensive success (Kisaalita et al., 2014).

The most common group of conditions/illnesses were (1) physical symptoms, (2) sleep issues and (3) mood disorders. A reason why physical symptoms (such as pain, itchiness, and excessive sweating) was selected could be due to prevalent ongoing current pharmacological treatment, and as a result, having accumulative and therefore more serious side effects (Ward et al., 2010; Turner & Connolly, 2018). Instead, open-label placebos can greatly reduce side effects. Treatment for sleep issues and mood disorders (such as the case of mild-moderate depression) have been reported in the literature as having no significant difference to placebo interventions (Kirsch, et al., 2008; Yeung et al., 2018). As a result, it is heavily debated whether condition improvement from these medications is due to the pharmacological treatment itself or the

placebo effect (Kirsch, et al., 2008; Yeung et al., 2018). Unlike placebo interventions, medications for sleep issues and mood disorders have a higher risk of side effects (e.g. addiction, nausea, drowsiness etc.; Kirsch, et al., 2008; Yeung et al., 2018). Additionally, they are expensive for the patient and the Australian Government (Fox, 2003). Open-label placebo interventions have the potential to be an effective substitute treatment, which would also eliminate some of the more serious side effects and costs associated with pharmacological treatment. Moreover, these findings may be applicable to the creation and future implementation of open-label placebos in clinical practice, by creating condition-specific or complaint-specific open-label placebos based on the aforementioned areas.

4.5 Hypotheses 1 – 6: Demographic influences on the likelihood to prescribe placebos

Results from the current study did not support the first hypothesis that females were more likely to prescribe open-label placebos compared to males. This did not align with the the United Kingdom study where female GPs were more likely to prescribe placebos (Howick et al., 2013). This could be due to findings that women were more likely to use positive suggestions and non-physical exams, which were specifically mentioned in the survey, whereas the present study only referred to the broad definition. Additionally, as the present survey was emailed out to academic GPs (AAAPC), this could be an explanation for why there were not gender effects. This is consistent with a previous study (Sherman & Hickener, 2008).

The second hypothesis was GPs who saw less patients per week would be more likely to prescribe open-label placebos, which was based on previous findings (Howick et al., 2013). This hypothesis was not supported by the current study. In fact, further research could indicate that the opposite is true; more patients seen per week can lead to additional placebo prescribing. This is

because GPs in the United Kingdom, Germany, and Poland studies saw on average 123, 250, and 140 patients per week respectively, and had a higher rate of placebo prescriptions (Babel, 2013; Howick et al., 2013, Meissner et al., 2012). This differs to the present findings in which only 20% of participants saw more than 100 patients per week.

The third hypothesis was based on Howick's (2013) proposal that the gender difference in placebo prescription rates could be a result of the number of days worked and consequently the number of patients seen per week. However, the present study did not find support for this. This could be due to the above reasons such as the lack of gender difference and patients seen per week.

The fourth hypothesis was that younger GPs would be more likely to prescribe open-label placebos compared to older general practitioners. This study showed that this result is not significant. Therefore, this does not support the results of previous research by Braga-Simoes (2015), who found younger general practitioners were more likely to prescribe placebos compared to their older counterparts. However, it does support other studies, which did not find an age difference (Meissner et al., 2012).

The fifth hypothesis was that years in practice would affect the likelihood of prescribing open-label placebos. These results were based on findings from Wartolowska (2014) and Baldwin (2016) who found that younger trainee orthopaedic surgeons were more likely to be supportive of placebo interventions compared to older senior orthopaedic surgeons. The results of the present study did not support their findings. Whilst a significant result was found in the two-way ANOVA, further post-hoc tests failed to find a significant difference between the groups. This means that there may be an effect here, however due to the small sample size (N=54) and lack of statistical power, it was not picked up. Future research with larger sample

sizes would benefit from investigating this further to see if it influences influence on the likelihood to prescribe open-label placebos.

The results of a two-way ANOVA did not support the sixth hypothesis regarding younger general practitioners being more likely to prescribe open-label placebos due to having spent less years in practice. Reasons for this could include the lack of significant results, as well as the study being underpowered and therefore potentially not reflective of the target population.

4.6 Research Question 4: Additional concerns and comments with open-label placebos

The last research question related to any additional concerns or comments GPs have around open-label placebos. One of the two most common concerns/comments reported was the importance of considering the open-label placebo from the patient's perspective. Comments regarding the patient's perspective included how accepting patients will be to open-label placebos, whether the patient will be able to give informed consent, and the potential misunderstanding of what an open-label placebo is.. These concerns from the patient's perspective, particularly with patient acceptability, is not novel with placebo interventions. As such, in a study examining the difference between GP and patient views towards traditional placebos, GPS underestimated how accepting patients would be to placebo interventions (Lynoe, Mattsson & Sandlund, 1993). A reason for this difference could be that the perception of prescribing a placebo intervention represents a socially undesirable behaviour due to negative ethical implications GPs may perceive. The second major concern/comment related to the lack of research into, and thus the lack of efficacy of, placebos. Once again, these comments are reflective of the current limited literature on open-label placebos (Charlesworth et al., 2017).

Further research is required to determine the efficacy of open-label placebos for a variety of conditions/illnesses.

4.7 Strengths and Limitations

A clear strength of this study is that it is the first to investigate medical practitioners' attitudes towards open-label placebos. This study specifically sampled GPs as they are an important stakeholder with placebo interventions due to reportedly being the highest placebos prescribers (Hassan et al., 2011). Therefore, understanding their current attitudes provides direction towards future research. This study is also a first in exploring attitudes towards traditional placebo interventions in Australia, therefore providing insight into the current behaviours in general practice. Questions administered enabled GPs to reflect on their own placebo prescribing behaviours and engage them in the placebo literature. Additionally, the items used to measure attitudes towards placebo interventions were adapted from previous experimental research, adding to the validity and reliability of these measures for future research into placebo interventions. Unlike previous studies, the present study provided open-ended questions, allowing participants to freely respond. This allowed deeper examination of the nuances of participants' beliefs regarding placebo intervention (Braun and Clarke, 2013)

Results from this study have contributed to existing knowledge in the current placebo literature and creates a platform for the direction of future research.

Despite these notable strengths, the present study was not without limitations. The main limitation of this study was the sample size. Reasons as to why there was the small sample size included it being a homogenous group (GPs in Australia). GPs, particularly compared to other

medical disciplines, typically have low survey response rates, as studies have found their responses have steadily declined for the past decade (Templeton, 1997; Cunningham, et al., 2015). GPs who declined to take part in the current survey provided reasons, such as inundation of surveys and not enough time. This echoes the previous finding that general practitioners' have reported survey burden, high volume of survey requests, the length of the questionnaire, insufficient background information, and the perceived value of the research as being reasons as to why there are low response rates (Cunningham, et al., 2015; Morris, Cantril & Weiss, 2001). Other factors include the location of the general practitioner, originating institution, being too busy to complete research, and being less qualified (Fielding, Clothier, Stocks & Kelly, 2005). Similarly, some medical practices have an office policy regarding participation in surveys (Wiebe, Kaczorowski & MacKay, 2012). In addition, the lack of incentive likely also affected the response rate. In a previous study, Gps who were offered a financial incentive were more likely to participate in surveys compared to those who were not (Crouch, Robinson & Pitts, 2011; Cunningham, et al., 2015).

Additionally, the use of a generalised, online survey tool could have also influenced the number of results. Online survey tools have the poorest response rate compared to other survey tools (e.g. postal surveys and telephone surveys), particularly when a personalised nature of recruitment is not used (Crouch et al., 2011).

Moreover, the data may not be representative of the whole population, as the sample gender distribution did not match the gender distribution of GPs in Australia. There is a roughly even split of registered male and female GPs in Australia (Medical Board of Australia, 2018), which is starkly different to the current survey where more women responded compared to males (65% vs. 35% respectively). This is in line with the current literature, which shows that it is

easier to recruit female participants for surveys and interviews in general compared to males (Slauson-Blevins & Johnson, 2016).

Another limitation is that the present study used self-report measure. There involves the risk that participants have been influenced by recall bias where there could be an underestimation/overestimation of answers to certain questions. Moreover, there was the delicate nature of the topic. As placebos are a grey area in modern medicine with strong ethical implications, general practitioners' may be wary about admitting support for placebo interventions, and whether they have prescribed a placebo in the past and/or the likelihood to prescribe an open-label placebo in the future The advertisement of the survey was included in the group (AAAPC). This group is for academic general practitioners' and therefore may prime some responses to be in support of open-label placebos due to them having an interest in research themselves, which could result in a sampling bias in the present study.

4.8 Future research

Future research should therefore look at overcoming the above limitations. Replication studies are needed to examine demographic influences using a more representative sample. Improvement to recruitment methods should look at including postal surveys, more personalised methods, and incentives in an attempt to increase participant response. This should allow the capturing of more perspectives and highlight any demographic factors that influence the likelihood to prescribe open-label placebos.

Further research into clinical trials with open-label placebos should use experimental conditions that involve physical symptoms (such as pain, itchiness, and excessive sweating), sleep issues, and mood disorders (such as depression, anxiety, and panic attacks) as reflected by

the commonly chosen areas by general practitioners. How general practitioners, amongst other medical professionals, can deliver the open-label placebo to both reduce deception and increase health outcomes also needs to be researched in further detail. More in-depth research looking at placebo usage in Australia can look at the different types of placebos used (e.g. impure vs pure) in a similar format to the other studies undertaken in the United Kingdom and Poland. This would lead to a deeper understanding of placebo-prescribing behaviours that the present study missed due to it not being a prime focus of this study. Overall, future research in this area can lead to rewarding outcomes and open-label placebos have the potential to become a successful treatment option.

Chapter 5: Conclusions

The current study provides meaningful insight into the currently under-researched area of open-label placebos. The study revealed that general practitioners' attitudes towards traditional placebos, compared to open-label placebos, only differed for those who were accepting of placebo interventions in the first place. The findings of the study showed strong support for psychological factors, such as expectations, and the patient/doctor relationship as the underlying mechanisms behind the open-label placebo effect. Additionally, this study suggests that Australian general practitioners would use open-label placebos in cases of non-specific or physical symptoms, which provides a valuable starting point in developing and implementing open-label placebos in clinical practice. Although no demographic influencers were found in the likelihood to prescribe open-label placebos, future research with larger samples could evaluate this further. These findings highlight concerns around the lack of research in this area and how

open-label placebos can be offered to a patient. Therefore, further research is necessary in both clinical trials and practice, to address these concerns.

Overall, as the cost and side effects of pharmacological treatment increases, open-label placebo interventions are a promising treatment option in clinical practice.

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Appendix 1

Participant Information Sheet

Dear Participant,

You are invited to participate in the research project investigating the attitudes of general practitioners towards open-label placebos, described below.

What is the project about?

Current literature looking at placebos and their effects support the idea that they can be beneficial for patients in clinical settings (outside of trials). Thus, it is important to determine under what conditions general practitioners in Australia think it is acceptable to provide placebos (if any), as well as exploring their current knowledge and experience of placebos, given with and without deceit. This project will explore these ideas through an online survey.

Who is undertaking the project?

This project is being conducted by Dr Elise Devlin PhD, Lecturer, XX XXXX B. Psychological Science, Honours candidate in the School of Psychology, and Dr. Oliver Frank MBBS PhD FRACGP FACHI, University Senior Research Fellow, Discipline of General Practice, Adelaide Medical School.

Why am I being invited to participate?

You are being invited as you are a practicing general practitioner in Australia.

What am I being invited to do?

You are being invited to participate in an anonymous online survey answering questions in relation to placebos, placebo effects and open-label placebos.

How much time will my involvement in the project take?

The involvement in the project is estimated to take between 10 and 15 minutes.

Are there any risks associated with participating in this project?

There are no foreseeable risks associated with participating in this project.

What are the potential benefits of the research project?

The potential benefits of the research project may result in a better understanding of open-label placebos in practice.

Can I withdraw from the project?

Participation in this project is completely voluntary. If you agree to participate, you can withdraw from the study at any time. As it is an anonymous online survey, you are able to withdraw before the submission of the survey.

What will happen to my information?

Participation in the survey is anonymous, data will not be matched to any identifiable information. The data may be published in journals and presented at conferences, however no individual result will be discussed, only combined data from all participants. Storage of the data will be kept on password protected machines at the University of Adelaide.

Your information will only be used as described in this participant information sheet and it will only be disclosed according to the consent provided, except as required by law.

Who do I contact if I have questions about the project?

Lead Investigator

Dr Elise Devlin

School of Psychology

Faculty of Health and Medical Sciences

[redacted]

[redacted]

XX XXXX

School of Psychology

Email: XX XXX

What if I have a complaint or any concerns?

The study has been approved by the School of Psychology: Human Research Ethics Sub-Committee (approval number H-2018-35). This research project will be conducted according to the NHMRC National Statement on Ethical Conduct in Human Research (2007). If you have questions or problems associated with the practical aspects of your participation in the project, or wish to raise a concern or complaint about the project, then you should consult the Principal Investigator. If you wish to speak with an independent person regarding concerns or a complaint, the University's policy on research involving human participants, or your rights as a participant, please contact Professor Paul Delfabbro on:
Phone: (08) 8313 4936
Email: paul.delfabbro@adelaide.edu.au
Any complaint or concern will be treated in confidence and fully investigated. You will be informed of the outcome.

If I want to participate, what do I do?
Participation is purely voluntary and can be undertaken by completing the following consent form and online survey.

Yours sincerely,
Dr Elise Devlin
XX XXXX
Dr Oliver Frank

Appendix 2

Consent form

I have read the attached Information Sheet and agree to take part in the following research project:

Title: General Practitioners attitudes towards placebos
Ethics Approval Number: H-2018-35

2. I have had the project, so far as it affects me, and the potential risks and burdens fully explained to my satisfaction by the research worker. I have had the opportunity to ask any questions I may have about the project and my participation. My consent is given freely.

3. Although I understand the purpose of the research project, it has also been explained that my involvement may not be of any benefit to me.

4. I agree to participate in the activities outlined in the participant information sheet.

5. I understand that as my participation is anonymous, I can withdraw any time up until submission of the survey.

6. I have been informed that the information gained in the project may be published in a thesis and potentially a journal article and conference presentations.

7. I have been informed that in the published materials I will not be identified and my personal results will not be divulged.

8. My information will only be used for the purpose of this research project and it will only be disclosed according to the consent provided, except where disclosure is required by law.

If you do not wish to participate in the research study, please decline participation by clicking on the "disagree" button.

- ○ Agree
- ○ Disagree

Appendix 3

Online Questionnaire

Demographic data

What is your gender?

- Male
- Female
- Other

Which category below includes your age?

- 25-39
- 40-54
- 55+

How long have you been a practising general practitioner?

- Less than 10 years
- 10-19 years
- 20-29 years
- 30-40 years
- More than 40 years

On average, how many patients do you see each week?

- Less than 25
- 25 to 50
- 51 to 100
- More than 100

Where did you complete your basic medical degree?

Australia

Other (please specify)

How would you describe your culture?

Western

Mostly Western

Both Eastern & Western

Mostly Eastern

Eastern

NEW QUESTION

Please read the following statement, which gives a definition of the placebo effect.

The term "placebo" refers to any intervention or treatment, that objectively is known to have no specific effect, but for which a beneficial outcome occurs as a result of the patient believing in its efficacy.

Do you agree with this definition?

Yes

No

If not, why?

Do you believe that placebos can be effective?

Yes

No

Don't know

Do you believe that placebo medicines/treatments can produce physical changes in the body'?

- Yes
- No
- Don't know

How much do you agree with the statement 'placebos can be delivered ethically'?

- Strongly agree
- Agree
- Neither agree nor disagree
- Disagree
- Strongly disagree

How much do you agree with the statement 'placebo medicines/treatments require deception in order to be effective'?

- Strongly agree
- Agree
- Neither agree nor disagree
- Disagree
- Strongly disagree

How much do you agree with the statement 'placebos have a place in clinical practice'?

- Strongly agree
- Agree
- Neither agree nor disagree
- Disagree

- ○ Strongly disagree

How likely would you be to prescribe a placebo for an adult?

- ○ Highly likely
- ○ Likely
- ○ Unlikely
- ○ Highly unlikely
- ○ Don't know

Do you have any concerns surrounding the use of placebos? If so, what are they?

[ ]

In your opinion, what is the mechanism behind the placebo effect? You may select more than one response.

- ☐ Psychological/ Expectations
- ☐ Patient/doctor relationship
- ☐ The natural course of the illness
- ☐ Conditioning
- ☐ Physiological
- ☐ Positive energies
- ☐ Unexplained factors
- ☐ Other (please specify)

In which of the following circumstances do you think the use of placebos is acceptable?

- ○ Permitted in both clinical practice and clinical research trials
- ○ Permitted only in clinical research trials

- Permitted in clinical practice if prior experience, within the department or personally, supports its efficacy
- Permitted in clinical practice if research supports its efficacy
- Always prohibited

How often have you prescribed or suggested a treatment with no active ingredients that you believe has a significant placebo benefit?

- Never
- Rarely (<1 per year)
- Occasionally (>1 per year)
- Often (>1 per month)
- Frequently (>1 per week)

NEW QUESTION

Recent studies have shown that placebos can produce beneficial effects even when patients are told that they are receiving placebos. In other words, deception is not necessary to achieve a therapeutic placebo response. This is referred to as an 'open-label' placebo.

Do you believe that open-label placebos can be effective?

- Yes
- No
- Don't know

Do you believe that open-placebo medicines/treatments can produce physical changes in the body?

- Yes
- No
- Don't know

How much do you agree with the statement 'open-label placebos can be delivered ethically'?

- ○ Strongly agree
- ○ Agree
- ○ Neither agree nor disagree
- ○ Disagree
- ○ Strongly disagree

How much do you agree with the statement 'open-label placebos have a place in clinical practice'?

- ○ Strongly agree
- ○ Agree
- ○ Neither agree nor disagree
- ○ Disagree
- ○ Strongly disagree

Would you ever consider the use of an open-label placebo in these situations? You may select more than one response.

- ☐ As a diagnostic tool (i.e. to distinguish between an organic and non-organic disorder)
- ☐ When all other therapies have been exhausted
- ☐ As a treatment for a non-specific symptom
- ☐ To calm a patient or to mollify a complaining patient
- ☐ To control pain
- ☐ Other (please specify) _____

Would you ever consider the use of an open-label placebo for these groups of illnesses/diseases? You may select more than one response.

- [ ] Physical illnesses (i.e. hypertension, cancer etc.)
- [ ] Physical symptoms (i.e. pain, itchiness and excessive sweating etc.)
- [ ] Mood disorders (i.e. anxiety, depression, panic attacks etc.)
- [ ] Sleep issues
- [ ] Other

How likely would you be to prescribe an open-label placebo for an adult?

- ○ Highly likely
- ○ Somewhat likely
- ○ Somewhat unlikely
- ○ Highly unlikely
- ○ Don't know

Do you have any concerns surrounding the use of open-label placebos? If so, what are they?

In your opinion, what is the mechanism behind the open-label placebo effect? You may select more than one response.

- [ ] Psychological/ Expectations
- [ ] Patient/doctor relationship
- [ ] The natural course of the illness
- [ ] Conditioning
- [ ] Physiological
- [ ] Positive energies
- [ ] Unexplained factors
- [ ] Other (please specify)

NEW QUESTION

Below are some different examples of verbal deliveries providers may give patients when providing a placebo. For each of the four options, select whether you feel the information given is acceptable and why.

Delivery 1: Patients are instructed to take two placebo pills, twice daily without any explanations of placebos.

- Yes
- No
- Additional comments

Delivery 2: The provider clearly explains that the placebo pill is an inactive substance like a sugar pill that contains no medication.

- Yes
- No

Additional comments

Delivery 3: The provider clearly explains that the placebo pill is an inactive substance like a sugar pill that contains no medication. Then explains the following four discussion points; 1) the placebo effect is powerful, 2) the body can automatically respond to taking placebo pills like Pavlov's dogs who salivated when they heard a bell, 3) a positive attitude helps but is not necessary, and 4) taking the pills faithfully is critical.

- Yes
- No

Additional comments

Delivery 4: The provider clearly explains that the placebo pill is an inactive substance like a sugar pill that contains no medication. Then explains the following five discussion points; 1) the placebo effect is powerful, 2) the body can automatically respond to taking

placebo pills like Pavlov's dogs who salivated when they heard a bell, 3) a positive attitude helps but is not necessary, 4) taking the pills faithfully is critical, and 5) previous scientific research supports the notion that open-label placebos are effective.

- ○ Yes
- ○ No

Additional comments

Thank you very much for taking the time and effort to participate in this important study on general practitioners attitudes towards placebos.

If you would like a summary of the results of this study, when they become available in the future, then please check the yes box below and we will be sure to email them to you.

- ○ No
- ○ Yes (please enter your email address)

Appendix 4

Email and Facebook Post

To Whom It May Concern.

I seek your help with a research project investigating the attitudes of general practitioners towards open-label placebos. This study is being conducted as part of an Honours project and aims to determine under what conditions (if any) general practitioners in Australia think it is acceptable to provide placebo medicines, as well as exploring their current knowledge and experience of placebo medicines, given with or without deceit.

The survey will take 10-15 minutes to complete.

Your participation in the survey is completely voluntary and anonymous, and your responses will be kept confidential.

Please click the link below to go to the survey Web site (or copy and paste the link into your Internet browser).

https://www.surveymonkey.com/r/6NLNC9J

Thank you very much for your time and cooperation.
Warm regards,

XX XXX B. Psychological Science

School of Psychology

University of Adelaide

Facebook post

Your views about the potential use of placebo medicines in clinical practice. Thanks to those members who have helped us by completing the survey. We are calling for more members to help us with this research.

The original post generated a lot of interesting discussion, which you can find by searching for 'placebo'.

In my University role, I am co-supervising an Honours psychology student, whose research project is about the potential uses of placebo medicines. Increasing our understanding of the potential uses of placebo medicines could lead to some useful new therapeutic strategies. I hope that you will help in this research. XX XXXX says:

*

I seek your help with a research project investigating the attitudes of general practitioners towards open-label placebos. This study is being conducted as part of an Honours project and aims to determine under what conditions general practitioners in Australia think it is acceptable to provide placebo medicines, as well as exploring their current knowledge and experience of placebo medicines, given with or without deceit.

The survey will take 10-15 minutes to complete.

Your participation in the survey is completely voluntary and anonymous, and your responses will be kept confidential. More details are in the first page of our online survey.

Please click the link below to go to the survey Website or copy and paste the link into your Internet browser.

https://www.surveymonkey.com/r/6NLNC9J

Thank you very much for your time and cooperation.

Warm regards,

XX XXXX B. Psychological Science

School of Psychology

University of Adelaide