Placebo Effects in Precision Medicine

Dasha A. Sandra

Department of Medicine

McGill University, Montreal

December 2021

A thesis submitted to McGill University in partial fulfillment

of the requirements of the degree of

Master of Science

Table of Contents

Abstract

Precision medicine is a new model of healthcare that focuses on customizing treatment for patient subtypes based on their biological characteristics. This approach can reliably improve treatment outcomes and patient health. However, it is unclear whether the process of treatment tailoring itself contributes to the better results by increasing patient expectations and resulting in a larger placebo effect. In this thesis, I propose that heightening individuals' expectations about the effectiveness of their treatment may improve intervention response.

To test this hypothesis, we conducted two studies. The feasibility Study 1 tested the role of expectations about treatment tailoring based on one's physiology. We recruited 17 participants to complete various medical tests, presented as either needed to tailor an analgesic machine to their profile or as a separate eligibility procedure. In reality, all tests were sham, and all participants received the same inactive placebo device. Participants then completed a pain task while using the placebo; those with a "tailored" treatment showed a trend towards experiencing more relief in pain intensity and unpleasantness. Study 2 translated this question into the field of precision psychiatry with 54 sub-clinically depressed young adults. We tested whether believing that physical exercise was chosen by an algorithm as best treatment for the participants' clinical case led to larger reductions in symptoms, as opposed to considering exercise a one-size-fits-all approach. Participants in the tailored group did not exhibit increased expectations and both groups improved at similar rates. This may have been due to ceiling effects of the intervention effectiveness and methodological limitations of expectation manipulation. Despite mixed results, our findings offer a promising avenue for further research testing the magnitude of the role of expectations associated with the treatment tailoring process on the resulting outcomes.

Keywords: precision medicine, placebo effect, expectations, contextual factors, pain, depression

Résumé

La médicine de précision est une nouvelle approche des soins de santé concentrant sur la personnalisation de traitement pour des sous-types de patients. Elle se base surtout sur leur caractéristiques génétiques et physiologiques. Une telle approche sur mesure peut améliorer de manière fiable les résultats du traitement et la santé des patients. Cependant, il n'est pas encore clair si le processus de personnalisation du traitement contribue à l'efficacité supérieure des traitements en augmentant les attentes des patients et en causant un effet placebo. Dans cette thèse, je propose que l'augmentation des attentes des individus concernant l'efficacité de leur traitement puisse améliorer la réponse à l'intervention.

Pour tester cette hypothèse, nous avons mené deux études. L'étude de faisabilité 1 a testé le rôle des attentes concernant l'adaptation du traitement aux caractéristiques physiologiques. Nous avons recruté 17 participants pour effectuer des divers tests médicaux, présentés soit comme nécessaires pour adapter un appareil analgésique à leur physiologie, soit comme une procédure d'éligibilité séparée. En réalité, tous les tests étaient fictifs et tous les participants ont reçu la même machine placebo inactive. Les participants ont ensuite complété une tâche de douleur tout en utilisant le placebo; ceux avec un traitement "sur mesure" ont montré une tendance à ressentir plus de soulagement de l'intensité de la douleur et des désagréments y associés. L'étude 2 a étendu cette question vers le domaine de la psychiatrie de précision auprès de 54 jeunes adultes sous-cliniquement déprimés. Nous avons testé si le fait de croire que l'exercice physique avait été choisi par un algorithme comme le meilleur traitement pour le profil clinique des participants entraînait une réduction plus importante des symptômes, au lieu de considérer l'exercice comme une approche standard. Les participants du groupe sur mesure n'ont pas manifesté d'attentes accrues et les deux groupes se sont améliorés à des taux similaires. Cela

a pu être dû aux effets de plafond de l'efficacité de l'intervention et aux limites méthodologiques de la manipulation des attentes. Malgré des résultats étant mixtes, ils offrent une voie prometteuse pour de nouvelles recherches testant l'ampleur du rôle des attentes de l'adaptation du traitement sur l'amélioration du patient.

Mots-clés: *médecine de précision, effet placebo, attentes, facteurs contextuels, douleur, dépression*

Acknowledgements

I would like to thank Dr. Mathieu Roy for supervising this project and giving me the flexibility, autonomy, and unenduring faith in my abilities that made these studies possible. He provided not only support for the current thesis, but also an open space to discuss a wide range of ideas, as well as much needed feedback to keep the projects realistic. I would also like to thank the members of my supervisory committee —Drs. Samuel Veissière and Jeff Mogil—for their brilliant ideas and unorthodox suggestions, without which the studies described here would not have happened. Finally, I would like to thank my colleague and friend Dr. Jay Olson for his contributions to this project, for helping me grow as a researcher, and for patiently hammering life lessons home over the years.

At the lab, I was lucky to be a part of a group of enthusiastic graduate students and would like to thank them for their contributions to this work: Todd Vogel and Sophie Desjardins for helping with the never-ending technical maintenance; Darius Velveticus for assisting with participant recruitment; Taryn Berman for discussing task details after all the pilot attempts; and Erika Gentile for providing critical insights into clinical populations. I would like to also thank the research assistants Mira Kaedbey, Victoria Stillitano, and Noah Furlani who have been instrumental in data collection.

Outside the lab, many thanks to my family and friends for their loving support throughout the entire degree, encouragement during the pandemic, and for providing fresh views on the questions tackled here. Specifically, thanks to Ekaterina Rossokhata and Jason Da Silva Castanheira for lengthy discussions on the merits of genetic testing and precision medicine which have inspired the work in this thesis. I would also like to thank my colleagues Alain Al

Bikaii, Despina Artenie, Mariève Cyr, Victoria De Braga, Jason Da Silva Castanheira, Denis Chmoulevitch, Élissa Colucci, Dr. Eric Jarvis, Dr. Oren Krajden, Dr. Mathieu Landry, Ekaterina Lunkova, Johnny Nahas, and Rémi Theriault for their helpful feedback on the project; Alain Al Bikaii, Denis Chmoulevitch, Johnny Nahas, and Rémi Theriault for being the brave pilot subjects and bearing many rounds of heat pain stimulation, and Dr. Jay Olson, Dr. Mathieu Roy, Dr. Jeff Mogil, Alain Al Bikaii, and Noah Furlani for their helpful feedback on this thesis.

The studies presented here received funding from the Fonds de Recherche du Québec: Science et Technologies (FRQNT) and were supported through the funds of Natural Sciences and Engineering Research Council of Canada (NSERC).

Contributions

Dr. Mathieu Roy, Dr. Jay Olson, Dr. Samuel Veissière and I designed the Study 1. Mira Kaedbey helped with obtaining the IRB approvals, piloting, data collection, and data transcription. I analysed the data.

For study 2, Dr. Jay Olson and I designed the study. Erika Gentile, Dr. Samuel Veissière, and Dr. Oren Krajden provided helpful suggestions on working with clinical populations. Victoria Stillitano and Noah Furlani assisted with obtaining ethics approvals, piloting, and data collection. Dr. Michel-Pierre Coll and Todd Vogel provided helpful feedback on data analysis. I analysed the study data and wrote the thesis. Dr. Mathieu Roy assisted with every step of the study and provided overall support for the thesis.

Chapter 1: Introduction

Precision medicine

Precision medicine is a novel healthcare approach that uses genetic, biological, and behavioural markers to develop more effective targeted therapies. Early use of these treatments has been successful in improving therapeutic outcomes in cancer treatment (Heinemann et al., 2013) and for cardiovascular disease medication dosing (Rieder et al., 2005). In precision oncology clinical trials, using a more targeted therapy has led to better overall treatment outcomes (Kato et al., 2020). Further, a drug combination based on specific physiological characteristics increased patient survival by 16 months for those with advanced stage breast cancer when compared to the standard treatment (Swain et al., 2015). For cardiovascular disease, the necessary dose for optimal response to common blood thinners may be based on one's gene variants (Rieder et al., 2005); these may be used to reduce severe side effects. The approach of using genetic and physiological tailoring is now expanding to neurodegenerative (Kovacs, 2016; Strafella et al., 2018), chronic (Agusti et al., 2016; Subramanian et al., 2020), and psychiatric disorders (Fernandes et al., 2017; T. R. Insel & Cuthbert, 2015).

Psychiatry can especially benefit from a more targeted approach. Contrary to the rest of medicine, many psychiatric disorders are diagnosed based on observable symptoms instead of underlying causes of disease, leading to subjective and heterogenous diagnoses with lower inter-practitioner reliability (Frances, 2013; Matuszak & Piasecki, 2012). In addition, mental disorders are often highly heterogeneous in subtypes and symptom combinations (Feczko et al., 2019). This leads to a lengthy period of diagnosis, trial-and-error treatment selection, and poor outcomes (Gaynes et al., 2009). A targeted approach could standardize the model of diagnosis

and treatment as well as bring it closer to the practices from other medical fields (Fernandes et al., 2017).

An early attempt at implementing precision psychiatry is the Research Domain Criteria Initiative (RDoC) from the National Institute of Mental Health. This approach proposes using a domain focus to mental illness, placing disorders at extremes of a continuous spectrum of functioning across different domains (Cuthbert & Insel, 2013). It also suggests a new framework for diagnosis based on results from large-scale studies testing pathophysiology (genetic, neural, and biological factors) instead of observable symptoms (Cuthbert & Insel, 2013; Insel et al., 2010; Insel, 2014). For instance, a recent review applying the RDoC model explored reward sensitivity as the underlying cause of mood-related symptoms in bipolar disorder, schizophrenia, and addiction (Nusslock & Alloy, 2017). It found distinct subtypes associated with depression, addiction, and bipolar disorders, which may now be used for choosing best treatments for specific patient profiles.

Researchers have also suggested using machine learning to determine specific subtypes and patterns in large patient datasets to predict treatment response (Bzdok & Meyer-Lindenberg, 2018). In one study of 43 schizophrenic inpatients a machine learning algorithm was able to predict anti-psychotic treatment response with 82.5% accuracy based on patients' brain connectivity (Cao et al., 2020). Another algorithm was able to determine lithium response to a clinically relevant degree in an international sample of 1266 bipolar patients (Nunes et al., 2020).

While precision approaches across the board show promise, they are generally in the early stages of development and implementation (Adams & Petersen, 2016). Further, it is unclear

how much of the observed increase in treatment effectiveness is due to the better precision as opposed to the effect of non-pharmacological factors like the patients' enhanced expectations.

Positive expectations

Holding positive expectations improves therapeutic outcomes via the placebo effect—the improvement from an inert substance or the broader therapeutic context (Frisaldi et al., 2020). Current literature uses the term of "placebo effect" to describe the net effect of an inactive treatment, which is different from the "placebo response" or the total response towards inactive treatment, including noise like independent improvement with time (Evers et al., 2018). Although the terminology of "placebo response" or "placebo effect" suggests a unified phenomenon, these are different types elicited by different methods (Benedetti, 2014; Benedetti, Pollo, et al., 2003; Bernstein et al., 2020; Colloca et al., 2004; Colloca & Barsky, 2020; Colloca & Benedetti, 2009; Finniss et al., 2010; Forsberg et al., 2017; Olson et al., 2021; Peerdeman et al., 2016).

For instance, a common approach to enhance expectations is to provide positive verbal suggestions about the treatment's effectiveness. Verbally suggesting the effectiveness of a placebo to healthy participants can reduce negative symptoms like pain perception (Forsberg et al., 2017), itch (Blythe et al., 2019), and many others (see Murray & Stoessl, 2013 for review). They may also be effective for clinical populations such as those suffering from chronic pain (Forsberg et al., 2017; Peerdeman et al., 2016). Positive suggestions for higher effectiveness are likely present in precision medicine and may unintentionally enhance patient expectations.

Pavlovian conditioning can also induce a potent placebo effect (Montgomery & Kirsch, 1997). For instance, an inert treatment can elicit a therapeutic response simply due to the

individual's prior experience with a similar-looking active one (Benedetti et al., 2007; Colloca & Benedetti, 2006). Both experimental (Amanzio & Benedetti, 1983) and clinical (Forsberg et al., 2017) pain demonstrate similar levels of therapeutic improvement from conditioning. Further, the effect is also present for patients suffering from clinical conditions such as Parkinson's disease (Quattrone et al., 2018), or Attention Deficit Hyperactivity Disorder (Sandler et al., 2010). Importantly, conditioned therapeutic response extends to more unconsciously regulated bodily processes, such as the immune system response (Price et al., 2007), and immunotherapy is a common target in precision medicine (Paucek et al., 2019). It is likely, then, that conditioning of expectations and response may play a role in the superior effectiveness of tailored treatments for some conditions.

Contextual factors in precision medicine

Beyond verbal suggestion and conditioning, various contextual factors may affect patients' expectations and induce a placebo effect (Bernstein et al., 2020; Colloca & Barsky, 2020; Finniss et al., 2010; Price et al., 2007). For example, social cues, experiential learning, physical décor, and the use of medical paraphernalia may all increase expectations independently or in combination (Bernstein et al., 2020). Some of these contextual factors may induce higher positive expectations about targeted treatments in particular. Indeed, patients may expect precision treatments to be more effective than the standard options (Issa et al., 2009; Miller et al., 2014). Tailored therapies may primarily boost expectations through the appeal to one's individuality and tailoring to biological characteristics. They are also more elaborate, come at a higher price, and provide the opportunity for a stronger therapeutic alliance – other elements well known to increase placebo effect in medicine.

Individual uniqueness

First and foremost, receiving a tailored therapy may potentially affect expectations by highlighting the individuality of the patient. In the public mind, tailored treatments are sometimes implicitly expected to be fully unique interventions designed for a particular individual (Juengst et al., 2016). If it existed, a treatment that implemented *all* the physiological particularities of a patient would indeed be more effective than a "one-size-fits-all" option. Rather, precision approach classifies patients in distinct groups based on their genetic and biological biomarkers. Still, the broader appeal of "unique tailoring" is salient in the public mind (Juengst et al., 2016). This may boost patient expectations in the broader context of rising individualism (Santos et al., 2017), desire for uniqueness (Cai et al., 2018; Ogihara et al., 2015), and the preference for personalized experiences (Deloitte, 2015).

Elaborateness

In precision medicine, tailoring a therapy to a patient is an elaborate process. Along with the usual diagnostic procedures, it requires one or several additional rounds of tests, like those for genetic biomarkers (Corcoran, 2020). The results of each test may then take up to several weeks to obtain and process (Rieder et al., 2005). Further, some of these tests, such as tissue biopsies, are more invasive than standard options (Corcoran, 2020). Studies in placebo science show that treatments that are more elaborate, time consuming, or use complex devices may lead to higher expectations and larger improvements (Kaptchuk, 2002; Kaptchuk et al., 2000, 2008, 2020). For instance, one study compared the use of acupuncture devices versus placebo pills and found devices to be more effective in reducing arm pain (Kaptchuk et al., 2006). The degree of invasiveness of the procedure also matters: sham injections, acupuncture, and surgery all elicit

better outcomes than sham pills (De Craen et al., 2000; Hróbjartsson & Gøtzsche, 2010; Meissner et al., 2013).

Price

Genetic testing and targeted therapies are also substantially more expensive. Tumor DNA sequencing can cost anywhere from $1000 to over $10 000 per test (National Cancer Institute, 2017), while precision therapies range up to $450 000 for more common cancers (Cutler, 2020) and $2.1 million for the rarer ones (Cutler, 2020; Rosenberg, 2019). These prices are much higher than those associated with standard therapies and may lead to expectations of a superior effectiveness. Indeed, a placebo described as more expensive elicited a better therapeutic response in both healthy (Waber et al., 2008) and clinical populations (Espay et al., 2015).

Therapeutic alliance

Finally, expectations can be more favourable for tailored treatments because the longer process allows to build a stronger therapeutic alliance. Fostering a positive doctor-patient relationship correlates with improved quality of life and medication adherence, as well as decreases in anxiety and depression (Kornhaber et al., 2016). More broadly, a warm and empathetic therapeutic encounter can improve outcomes for both active and inactive treatments in experimental (Howe et al., 2017) and clinical (Blasini et al., 2018) settings. Some studies have found that high perceived warmth and competence from a provider can modulate the magnitude of the placebo effect for inactive treatments Howe et al., 2017). Choosing a tailored treatment requires more medical visits than a standard option, giving the physician additional opportunities to foster warm therapeutic encounters and develop a positive relationship with each patient. Further, providing enhanced information about the treatment can improve the outcomes for already potent drugs like opioids (Amanzio et al., 2001; Benedetti, Maggi, et al., 2003). In one

study, post-operative patients receiving opioids intravenously openly from a doctor who described it as a powerful painkiller showed an approximately 50% larger increase in pain relief when compared to a group receiving it unknowingly from a machine (Amanzio et al., 2001). Another study conducted by a different research group at a different hospital showed similar effects (Benedetti et al., 2003). In precision medicine, practitioners need to clearly communicate complex information about the treatment's mechanisms and possible effectiveness to the patients. Treatment teams may therefore involve genetic councillors, who are better trained to educate patients and address their psychosocial concerns (Austin et al., 2014; Kohut et al., 2019), thus combining the benefits of enhanced communication and therapeutic alliance.

Although precision medicine combines these contextual factors with the potential to increase patient expectations, no studies to our knowledge have explored their role in the overall precision treatment effectiveness. Understanding the influence of personalisation process as a placebo response-inducing factor is important for two reasons. First, it would inform research methodology in precision medicine research and suggest the possible proportion of placebo response in the enhanced treatment outcomes. Second, if the placebo effect of tailoring is indeed present and considerable, it could be potentially harnessed through clinicians' emphasizing the personalised features and thus increasing potential therapeutic improvement.

Present work

This thesis includes two studies. In Chapter 2, I focus on the role of personalisation expectations in the context of general precision medicine using genetics and physiology as basis for treatment tailoring. I present a lab-based feasibility study exploring the effect of expectations of treatment tailoring on pain relief for healthy participants. Here, we tested whether participants experienced stronger pain relief when believing that their treatment was tailored to their

physiology. Chapter 3 extends the same research question to the context of precision psychiatry, tailoring through artificial intelligence, and a subclinical population. In an online study, we explored whether believing that an intervention is tailored to one's health and clinical profile by an algorithm leads to larger reductions in depressive and anxiety symptoms. Combined, these two studies show a promising avenue for research on expectations in the era of personalisation, and their potential implications for the nascent field of precision medicine.

Chapter 2: Expectations of tailoring to physiology for pain relief

Introduction

Tailoring to physiology

Currently, precision treatments are primarily tailored to one's genetics and biological characteristics. These characteristics are often believed to define a person's essence due to the *genetic essentialism* bias—a belief that living organisms have underlying features that determine their fundamental nature (Gelman, 2003, Dar-Nimrod, 2011). Such a cognitive heuristic provides an attractive simplification for complex human behaviour. It further associates genetic factors with the idea of uniqueness and can therefore boost expectations about the effectiveness of treatments tailored to these.

Interpretation of information through the lens of genetic essentialism may induce strong expectations on perception and attitudes, leading to changes in attitudes, behaviour, and physiology. Studies have primarily focused on the negative influence of such interpretations. For example, biologically based explanations of disease are often considered to be less controllable. Experiments testing beliefs about obesity find that genetics-based explanations of the condition reduce self-efficacy and perceived control over one's weight (Beauchamp et al., 2011; Dar-Nimrod et al., 2014). Other evidence shows participants eating substantially more after they are presented with a genetics-based explanation for obesity, as opposed to a psychosocial explanation (Dar-Nimrod et al., 2014). Finally, genetic essentialist mindset may decrease physiological abilities, regardless of whether the genetic risk is real or not (Turnwald et al., 2019). In two experiments with a total of 223 healthy individuals, researchers provided participants with a sham genetic risk assessment and suggested some to be at risk for obesity

(Turnwald et al., 2019). As a result, participants experienced a decrease in their cardiorespiratory ability, running endurance during exercise, physiological satiety levels, and perceived fullness after food consumption. These changes were also larger in magnitude than those predicted by participants' actual genetic risk for developing obesity.

Effects of genetic and broader biological essentialism on expectations and health go beyond obesity. Depression, an illness that is widely considered by the public to be due to brain changes (Pescosolido et al., 2010), shows similar negative effects on perceived control, behaviour, and clinical symptoms (Ahn et al., 2020; Kemp et al., 2014; Lebowitz, 2019; Lebowitz et al., 2013; Lebowitz & Ahn, 2015). Luckily, emphasizing the malleability of depression due to environmental factors reduces these effects and improves symptom outcomes in subclinical populations for several months (Lebowitz & Ahn, 2015).

Given the breadth of evidence for the negative influence of biology-based suggestions on physiology and behaviour, positive suggestions of biology-based tailoring may show similar effects in the opposite direction. Indeed, in the same study by Turnwald and colleagues (2019), the suggestions of genetic protection against obesity showed positive effects on several physiological measures. Similarly, tailoring a treatment to one's genes and physiology may provide powerful positive expectations about its effectiveness.

Aims and hypothesis

Here, we explored the role of whether these positive expectations would increase actual intervention response. In a feasibility study, we presented our participants with a placebo described as a powerful analgesic treatment, collected samples for genetic and skin conductance testing, and later, for some of them, pretended to adjust the analgesic features and dose based on

their individual biological characteristics. The testing session involved an elaborate medical procedure with multiple contextual cues (see Figure 1): the study location (McGill University Genome Centre), various medical paraphernalia (e.g., lab coats, badges, latex gloves), therapeutic alliance (warm and friendly experimenters), and the nature of the placebo itself (a large electric device with blinking lights, sounds, and multiple dials). This procedure was important to increase the believability of the placebo and maximize the effectiveness of general non-specific factors for all participants (Olson & Raz, 2021). Indeed, various researchers have independently suggested to combine contextual factors to increase placebo effectiveness. For example, several constructs from social psychology such as priming, expectations, and practitioner warmth could enhance placebo effects in psychotherapy (Sliwinski & Elkins, 2013). Additionally, combining décor and physician attire could affect the general magnitude of placebo effects (Bernstein et al., 2020), diagnostic process and clinical interactions may add to the improvements in acupuncture (Paterson & Dieppe, 2005), and an elaborate ritual with therapeutic communication can enhance pain analgesia in Irritable Bowel Syndrome patients (Kaptchuk et al., 2008). The combination of factors used in this experiment draws from a recent feasibility study which combined various contextual factors like medical context, elaborate ritual, therapeutic communication, and social proof into an intentionally elaborate "placebo machine" procedure to enhance the placebo effects (Olson et al., 2021). We used a similar combination to convince participants about the effectiveness of a personalised placebo machine intervention to reduce pain.

We hypothesized that the chosen combination of a placebo machine, genetic testing, and medical setting will be credible and effective in inducing large placebo effects. We also expected that perceiving the treatment as individually tailored based on various genetic indicators will lead

to larger reductions of reported pain intensity and unpleasantness. If our results are as predicted, emphasising uniqueness of tailored treatment may provide a potential strategy to additionally increase their effectiveness and reduce the side effects.

Methods

Participants

Inclusion and exclusion criteria

We recruited participants from the McGill University community, aged 18-35, with normal vision, fluent in English, not currently taking any painkillers or mind-altering drugs, and without prior diagnoses of skin conditions, pain, or diabetes. We considered an individual dataset to be full (and thus to contribute to our sample size) if the participant had no missing data on the ratings of pain intensity or unpleasantness and has no other exclusions (see below). We also planned to exclude participants if they indicated suspicion about the relevant parts of the study (e.g., the placebo device or the personalisation procedure).

Sample characteristics

In total, 19 participants between 19 and 31 years old from the McGill University community volunteered for the study. One participant was excluded from the final sample due to technical errors during testing, and another one for guessing the placebo component. The final study sample thus included 14 women and 3 men ($N = 17$), with an average age of 21.12 ($SD = 2.89$); most were Caucasian ($n = 6$) or Asian ($n = 6$) undergraduate psychology students ($n = 9$). There were 10 participants in the experimental group and 7 in the control, and the recruitment was halted due to the COVID-19 pandemic.

Design

The study was approved by the McGill Review Ethics Board-II (#45-0619). In a mixed-design experiment, participants came to the lab ostensibly for a study on painkillers and meditation practice (see Figure 1 for full design). They completed several (sham) medical tests that they believed would determine their eligibility for the study: blood pressure, a genetic test using a cheek swab, an electric skin conductance test, and a pain threshold test. Participants were then randomly assigned to either the experimental or control group. Those in the experimental group learned that the results from their tests would be used to tailor the (placebo) painkiller to their biological profile, thus maximizing its effectiveness; they also learned more about the painkiller itself. The experimenter then provided them with false genetic feedback as a part of the "customization" procedure. In the control group, the experimenter briefly described the common kinds of pain killers used in medicine instead (see Appendix A for the full script). Participants in both groups then met the second experimenter, who was blind to their condition, and completed the actual data collection. She led participants through a computerized pain task in which they received heat pain stimulations on their forearm and rated the perceived pain intensity and unpleasantness. During half of the testing session, participants also received the placebo analgesic that was either customized to them or presented as standard. Prior to debriefing, experimenters assessed participants for suspicions about the true nature of the study.

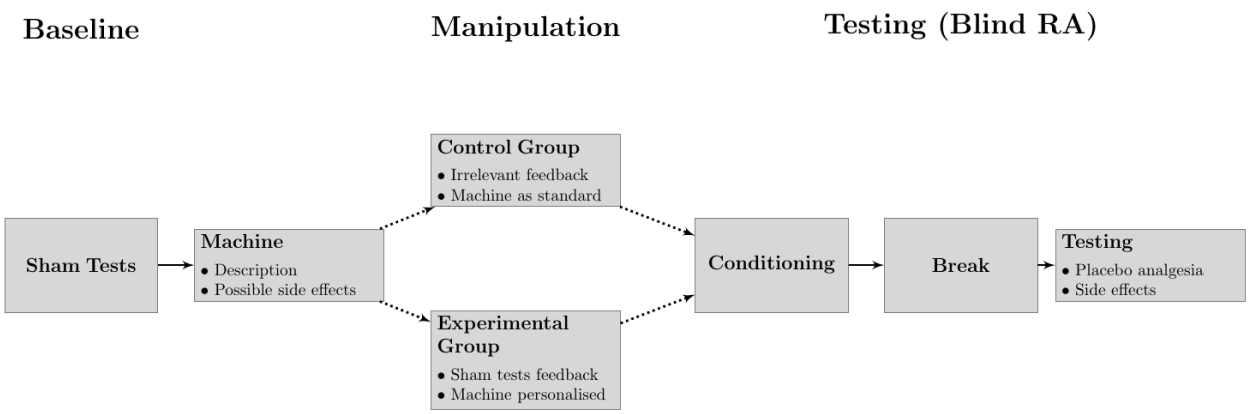


Figure 1. Study 1 design. Participants in both groups rated their expectations about treatment effectiveness after the conditioning and immediately prior to the testing session.

Procedure

Briefing

Participants met the technician wearing a white lab coat in the lobby of the McGill Genome Centre, to participate in a study ostensibly focusing on meditation practice and painkillers. They followed the technician to the testing room (Figure 2A) to meet the experimenter (also in a lab coat), learn about the details of the study, and test the analgesic machine, introduced as Alpha-TENS (Figure 2B). Participants also learned that the study would only start after successfully completing all the medical tests (blood pressure, skin conductance, genetic biomarkers, and pain threshold tests) which were presented as "standard for these kinds of studies." Throughout the session both experimenter and technician smiled, maintained eye contact, and acted in a friendly and caring way to foster therapeutic alliance (Howe et al., 2017).

Figure 2. The general setting for the testing session (A) and the placebo Alpha-TENS device (B).

Medical tests

After signing the consent form, participants provided a cheek swab sample for a genetic test, following the typical procedure one would go through at a hospital (i.e. experimenter wearing surgical gloves and carefully handling the sample as to not contaminate it (Olson & Raz, 2021). Moving on to the next test, the experimenter attached the electrodes to the participants' arm and pretended to monitor their electrodermal signal using a BIOPAC system (BIOPAC Systems Inc., Goleta, CA). This would be ostensibly to confirm that it was indeed safe for the participant to use the Alpha-TENS.

The participant then answered several questions about their background, ethnicity, use of medication, and prior meditation experience to further reinforce the cover story of the study focusing on meditation effects. If participants had meditation experience, the experimenter asked for further information concerning the length, frequency, and type of practice.

Pain threshold

Next, participants completed the computerised sensory calibration task, to detect their personal thermal pain threshold (Tabry et al., 2020). To make them more comfortable, the experimenter explained the process and type of pain stimulations in detail, as well as marked the spots where the pain was to be applied. She explained that the participants would receive thermal pain stimulations on one of the four spots on their inner forearm at a time, chosen in advance at random, and were asked to rate the pain on numeric scales between 0 and 100 on dimensions of pain intensity and unpleasantness. If participants asked to stop the pain stimulation before it finishes, we excluded the ratings of that specific trial from the pain threshold calibration.

Finally, participants completed several questionnaires measuring different personality traits or to reinforce the cover story: Need for Uniqueness Scale (NUS, Snyder & Fromkin, 1977), Multidimensional Assessment of Interoceptive Awareness (MAIA, (Mehling et al., 2012), Big Five Inventory (BFI, John et al., 1991; John & Srivastava, 1999), Fear of Pain Questionnaire-III (FPQ-III, McNeil & Rainwater, 1998), and Pain Catastrophizing Scale (PCS, Sullivan et al., 1995).

Tailored feedback

Once participants completed medical tests, they were randomly assigned to either the tailored feedback or control condition. In the tailored feedback condition, the experimenter began by mentioning that the results of the tests can be used to tailor the analgesic machine to each person's individual biological profile. She suggested that, although the machine was effective as is, she could further personalize it for "maximum effectiveness." Before doing so she showed and explained the false genetic results to the participants (see Appendix B for the false feedback). The experimenter also explained the functioning of the machine itself in detail, describing it as "a powerful analgesic developed in 1980's that works by reducing local nerve signalling." (Thus, the vintage exterior of the machine and the need to use a device instead of a pill or cream was rationalised for participants, see Appendix A for full script). She then adjusted several dials on the machine while consulting the participants' test output and demonstrated the personalised machine in action to ensure their comfort and positive expectations. She placed both the electrodes on the participants' left arm above the pain stimulation spots and turned the machine on (which was accompanied by the characteristic flashing lights and vibrating sound to reinforce the appearance of the machine working).

Control condition

For participants assigned to the control group the procedure was largely the same but without elements of personalisation. The experimenter received the genetic feedback for the participant and then discarded it after a cursory check, informing the participants that they were eligible for the study. She then described the different kinds of analgesics currently used in healthcare, as well as asked the participant about previous painkiller use (if any), to control for potential positive effects of attention and therapeutic communication (Howe et al., 2017). Then, she introduced the machine with the same description and demonstration (without adjustments) as in the personalised group.

Pain task

To reduce potential demand characteristics, the technician who blind to the testing condition, replaced the experimenter for the actual data collection. The two experimenters had no contact throughout the session. Participants then completed 18 trials in four blocks of four trials (with 2 practice trials after the first two blocks)—two conditioning and two testing. Each trial consisted of a heat stimulation lasting 9 seconds (2.5 s temperature ramp-up, 4 s full temperature stimulation, 2.5 s ramp-down at rate of 2.3 °C/s). The stimulation was applied at one of the same four spots used for the sensory calibration task, in random order.

During the first two blocks we conditioned the placebo response, with one block including the placebo machine. For the placebo-off block participants received their level 80 heat pain (on a 100-point scale). For the placebo block, they received level 20 pain (Wager et al., 2004, 2011); the "machine on-off" order was the same across all participants. Thermal pain stimulations sometimes cause sensitization and habituation that introduces noise in the results

(Jepma et al., 2014). To avoid it, we applied heat stimulations randomly only on areas 1 and 3 of the participants' arm for the conditioning phase, leaving the spots 2 and 4 for the testing phase.

For the remaining two blocks, the technician applied heat to the areas 2 and 4 on the participant's arm. She first ran 2 habituation trials, and then completed the remaining two blocks of the task, with order of placebo machine state (on-off or off-on) counterbalanced and level 50 of heat pain. We expected that the difference in participants' pain perception between the block without the placebo and the one with it will result in the magnitude of placebo analgesia.

Assessment of expectancy and debriefing

Throughout the pain task, participants also rated their expectations about the effectiveness of the machine on a 10-point scale (where 1 is "Not at all effective" and 10 is "As effective as possible"). They rated it on 2 occasions: after the conditioning phase (T_1), as well as before (T_2) the block with the placebo machine on.

Once all measurements were completed, the experimenter and technician interviewed participants about their experience, probed them for suspicion about the true purpose of the study (Nichols & Edlund, 2015), and provided partial debriefing. All participants were debriefed after the completion of the study.

Materials

The participants completed all the computer tasks on a standard lab computer. The calibration task was done using E-Prime (Psychology Software Tools, Inc., Sharpsburg, PA), MATLAB R2020b (The Mathworks, Natick, MA) for pain sensitivity curve calculations, and a MEDOC Pathway heat stimulator (TSA-II Neurosensory Analyzer, Medoc Ltd. Advanced

Medical Systems, Israel) for heat stimulations. The test pain task and questionnaires were delivered through PsychoPy 3.1 software (Peirce, 2009).

Measures

Need for Uniqueness Scale (NUS)

The NUS is a 32-item self-report measure assessing a person's motivation to appear different or unique (Snyder & Fromkin, 1977), and may potentially moderate the effect of expectations associated with treatment tailoring. Participants rate characteristics like "Feeling 'different' in a crowd of people makes me feel uncomfortable" on a scale of 1 (Strongly Disagree) to 5 (Strongly Agree). It has a high internal reliability (Cronbach's $\alpha = .84$).

Big Five Inventory (BFI)

The BFI is a 44-item self-report measure assessing five broad personality traits: openness to experience, conscientiousness, extraversion, neuroticism, and agreeableness (John et al., 1991; O. John & Srivastava, 1999). Participants rated characteristics like "I am someone who is talkative" on a scale of 1 (Disagree Strongly) to 5 (Agree Strongly). It has good internal reliability (Cronbach's $\alpha = .83$).

Fear of Pain Questionnaire-III (FPQ-III)

Pain anxiety and desire for pain relief may predict the magnitude of placebo analgesia experienced (Wager, 2005). The FPQ-III is a 30-item self-report measure assessing fear in response to painful stimuli (McNeil & Rainwater, 1998). Participants rate painful experiences such as "Breaking your arm" on a scale of 1 (Not at all) to 5 (Extreme). Subscales have excellent internal consistency, ranging from Cronbach's $\alpha = .88$ to .92.

Pain Catastrophising Questionnaire (PCS)

The PCS is a 13-item self-report measure assessing the trait for catastrophizing thoughts related to pain (Sullivan et al., 1995). Participants rate thoughts and feelings such as "I feel I can't go on" about the experience of pain on a scale of 1 (not at all) to 4 (all the time). The higher the score, the more catastrophizing thoughts are present. This questionnaire has excellent internal consistency of Cronbach's $\alpha = .93$.

Calibration Task

This task allowed to determine participants' pain sensitivity curve to calibrate their individual levels of pain to be used for the pain task (Tabry et al., 2020). The experimenter marked four locations on the participants' inner forearm, 3 cm in length each, which indicated the four positions for heat stimulation. The heat was delivered via the Medoc Pathway heat stimulator thermode (3x4 cm large). Participants completed 28 heat stimulations, with seven temperatures ranging from 40°C to 49°C for each arm spot. Each stimulation was applied to one of the four locations predetermined at random. This generates the participant's pain sensitivity curve and extracts each participant's self-reported level 20 (low), level 50 (medium) and level 80 (high) of pain. Each heat stimulation lasted 9 seconds (2.5 s ramp-up, 4 s max temperature, and 2.5 s ramp-down at the rate of 2.3 °C/s). Participants first indicated whether they felt heat or pain; if rated as heat, they assigned it a score on a visual-analogue scale of 0 (No warmth at all) to 100 (Very hot without pain). If painful, they rated its intensity on a visual analogue scale of 0 (No pain at all) to 100 (Extremely painful) and also rated the pain unpleasantness on a similar scale. The pain intensity describes how strong the sensation was, and the pain unpleasantness indicates how much the sensation was emotionally bothersome. The task took approximately 20 minutes.

Analysis Plan

We had two main hypotheses for this study. First, we expected participants in the tailored placebo group to show higher expectations of machine effectiveness at the end of the conditioning session. To test this hypothesis, we used a one-tailed t-test. We only tested the differences at T_2, which represented the final participant expectations prior to using the placebo.

Secondly, we also expected participants in the tailored placebo group to show a larger placebo response than those in the control group due to the perceived personalisation. We used a mixed-effects linear regression and conducted two separate tests. We separately tested the main outcomes of pain intensity and unpleasantness given the condition (tailored or control), placebo machine state (on or off), and the interaction between the two. The participant was used as a random factor. We tested only the interaction for each test, using Type I error rate of 0.05 and one-tailed tests.

Results

Expectations

Both groups had similar expectations about the effectiveness of the placebo at first assessment (T_1). The experimental group had an average rating of 5.8 out of 10 ($\mathrm{SD} = 2.39$), and the control group a rating of 5.6 out of 10 ($\mathrm{SD} = 2.07$). The expectations stayed the same prior to the device use ($T_2, M_{exp} = 7.5\ (2.01), M_{control} = 7.3\ (1.70)$). The differences at T_2 were not significant, $t(16) = -0.24, 95\%\ \mathrm{CI}\ [-1.81,\ 1.33],\ p = .59$.

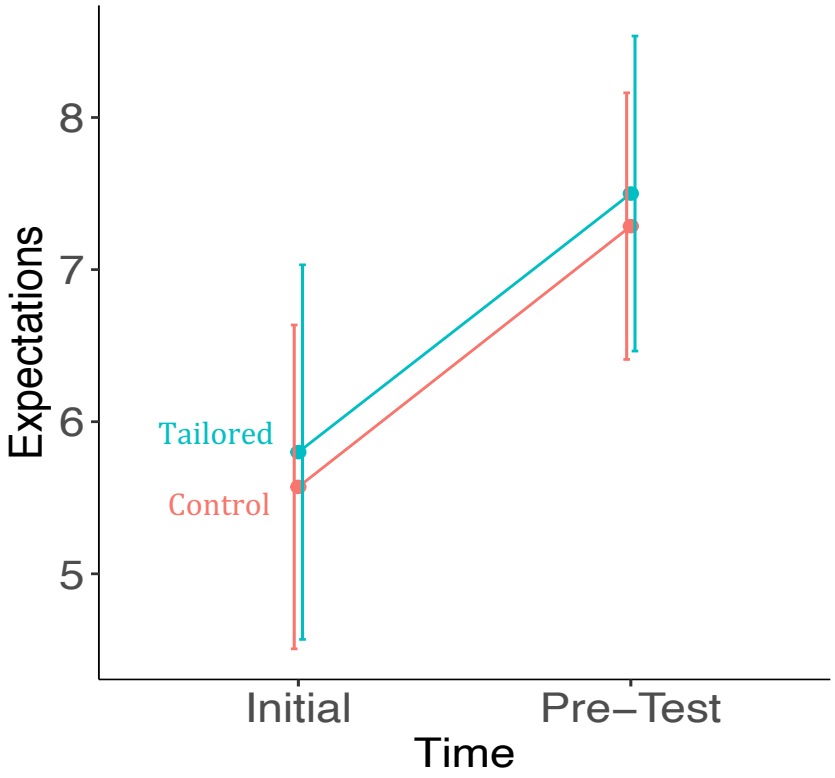


Figure 3. Evolution of participant expectations related to the effectiveness of the placebo machine. Participant expectations were assessed after the conditioning procedure (Initial) and immediately prior to testing (Pre-Test). Error bars indicate 95% CIs.

Pain Ratings

Participants receiving a tailored placebo reported on average a 21.13-point reduction in pain intensity on a 100-point scale, compared to the control group with a 5.1-point reduction; however, the results were non-significant (standardized $b = -0.62, 95\%\ \text{CI} = [-1.55, 0.32]\ p = .13$; Figure 4A). We found similar results for pain unpleasantness. Participants in the experimental group reported a higher reduction of 25.03 points compared to the controls with 6.95 points ($b = -0.61, [-1.36, 0.13], p = .09$; Figure 4B). The differences in pain unpleasantness were also not significant.

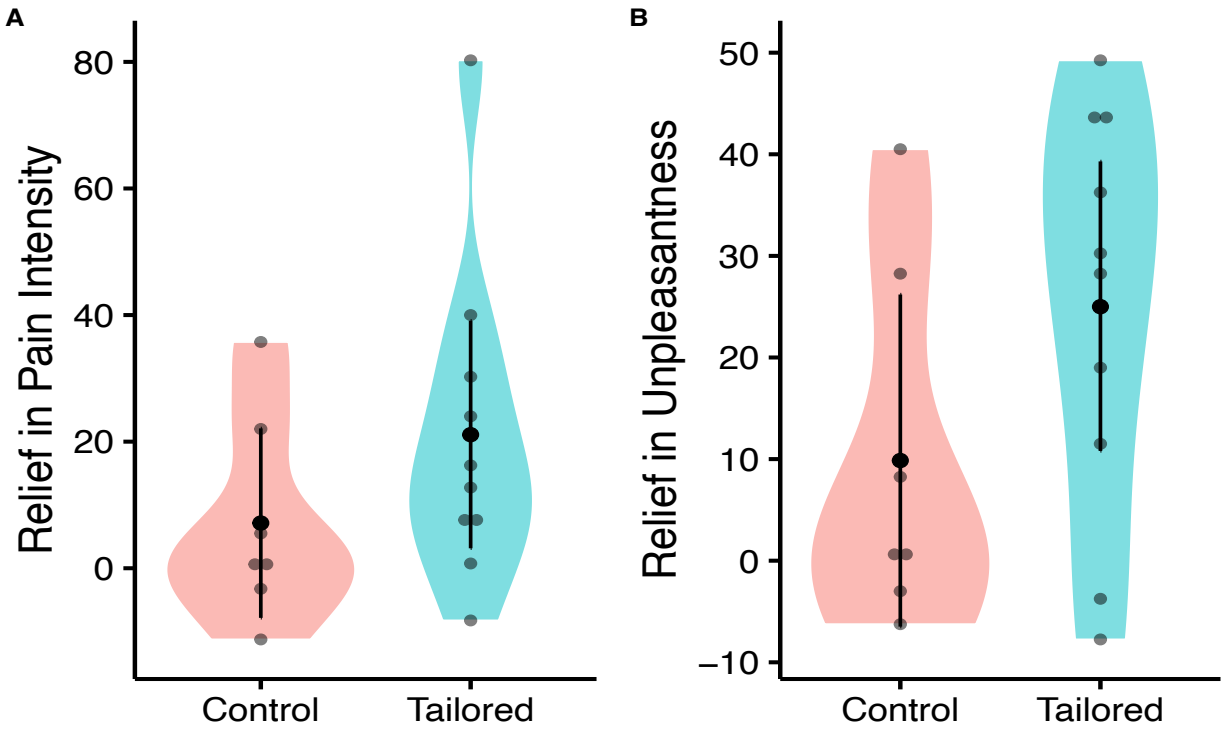


Figure 4. The average (and individual) changes in ratings on pain intensity (A) and unpleasantness (B). Error bars indicate 95% CIs.

Discussion

We found potentially promising results in a small pilot study testing the effects of expectations associated with a biological treatment tailoring. Although all findings were nonsignificant, participants tended to show a greater relief on pain intensity and an even larger one for the pain unpleasantness from a tailored placebo. The results on pain unpleasantness are in line with previous findings in the literature; indeed, studies found pain anxiety and the desire for relief to be important moderators of placebo analgesia (Wager, 2005).

Limitations

A major limitation of this study is its small sample size due to restrictions associated with the COVID-19 pandemic. Indeed, although the effect sizes appear to be large in our pilot sample, it is likely an overestimate due to the inflation of small samples (Button et al., 2013; Ioannidis,

2008). The actual effect size of the personalisation expectations is likely present but smaller and needs to be further investigated in large and representative samples.

Further, participants in both groups exhibited similar expectations regarding the effectiveness of the treatment. While this is potentially an important caveat that speaks to the manipulation check of the effectiveness of our procedure, it must be taken in the broader context of an extremely small sample size and the high score variability. In other words, we need a larger sample before we can conclude any measurable effects on expectations or pain relief.

Finally, we used an inactive placebo as opposed to a real treatment, which may have limited the applicability of our results. Placebo effects are often believed to be additive to the proportion of the effect of the real drug (Beecher, 1955; Boehm et al., 2017); this assumption underlies the randomized control trial approach being the gold standard for testing medication effectiveness (Cartwright, 2007). However, scholars suggest that the placebo response may instead interact with that of the drug in complex and unpredictable ways, for example by enhancing, maintaining, or decreasing active drug effects differently for different patients (Boehm et al., 2017; Fava et al., 2017). In fact, it is possible that "tailoring" an inactive placebo instead of a real medication may *limit* the potential increase in effectiveness. Active treatments often produce side effects and physiological sensations which may be interpreted as a signal that the treatment is working (Kirsch & Sapirstein, 1998). These are absent from inert substances. Indeed, a major reason for placebo unblinding in clinical trials—participants guessing they are in the placebo group—is due to the lack or low levels of experienced side effects in the inactive placebo group (Moscucci et al., 1987). Inactive placebos therefore may be a good option for testing the feasibility of the study, but one cannot rely on findings obtained from using them to reliably extrapolate effects of expectations to real treatments.

Strengths

Despite the non-significance of our results, the study points in a promising direction. Our experiment was double-blind, thus reducing the potential for demand characteristics or response bias and increasing the validity of participant pain and expectation ratings. Indeed, response bias is a major limitation of many placebo studies and reduces the validity of their results (Hróbjartsson et al., 2011). Further, our testing and tailoring procedure was also credible: all participants but one believed in the veracity of the device, and none guessed the sham personalisation component. This suggests the feasibility of this procedure beyond what was previously reported (Olson et al., 2021) and the usefulness of the general principles of complex deception for placebo research (Olson & Raz, 2021). In the next chapter, we use some of these general principles further to conceptually replicate our research question and to generalize the role of expectations in precision medicine. Here we focus on a particular branch of medicine—precision psychiatry—and on depressive symptoms in young adults.

Chapter 3: Expectations of personalisation in depressive symptoms

Introduction

Characteristics of depression

Depression affects 265 million people worldwide (World Health Organization, 2020). It is the leading cause of disability in the world, is called the "common cold" of psychiatry, and is often comorbid with other psychiatric or physical illnesses (World Health Organization, 2020; Goodwin, 2006). Approximately 10.8% of people will experience depression at some point in their life (Lim et al., 2018), with rates in the United States and Canada at 20.6% and 12.2%, respectively (Hasin et al., 2018; Patten et al., 2006). Further, women of childbearing age are twice as susceptible to depression than men (Albert, 2015; Kessler, 2003; Weissman & Olfson, 1995).

Depression can present as a standalone disorder (a major depressive disorder or episode) or be comorbid with other medical conditions (American Psychiatric Association, 2013). A major depressive episode is characterized by several types of affective and physical symptoms that persist for at least two weeks, cause substantial distress, and reduce a person's normal functioning. Depression is a multifaceted syndrome with clinical profiles including combinations of mood disturbances, reduction in sleep quality, reduction or increase in sleep duration and appetite, decrease in feelings of pleasure, psychomotor symptoms, feelings of guilt, anhedonia, and presence of suicidal ideation(American Psychiatric Association, 2013).

Standard treatments for depression

The first line of treatment for depression includes antidepressant medication, psychotherapy, or a combination of both (Gelenberg et al., 2010). Antidepressants are a common first line treatment for depression (Cipriani et al., 2018). They are believed to work through rebalancing specific neurotransmitters in the brain, yet their mechanisms of action are still not entirely understood (Harmer et al., 2017). The other standard treatment for depression is psychotherapy. There are dozens of different types of psychotherapy with similar levels of effectiveness, according to some meta-analyses (for review see Cuijpers et al., 2019). Although researchers still debate whether psychotherapy is superior to antidepressant treatment (de Maat et al., 2006; Imel et al., 2008; Spielmans et al., 2011), they agree that a combination of medication and psychotherapy is preferable to either type of treatment alone (Cuijpers et al., 2014, 2015; Kamenov et al., 2017).

Exercise as treatment for depression

Medical associations and public health agencies often recommend exercise as a third treatment option or as a treatment adjunct for milder depressive symptoms (Davidson, 2010; Rimer et al., 2012). Physical exercise is highly effective in treating mild and moderate depression (Cooney et al., 2014; Craft & Perna, 2004; Kvam et al., 2016; Rimer et al., 2012). In one study, 202 adults suffering from Major Depressive Disorder were assigned either to antidepressant treatment with sertraline, supervised exercise, a home-based exercise program, or placebo pills for 16 weeks. All but those in the placebo group showed similar rates of remission from depression (Blumenthal et al., 2007). An earlier study with older adults showed similar results (Blumenthal et al., 1999). Finally, exercise can also at times be effective as an addition to

pharmacotherapy for severe depression (Schuch et al., 2011, 2015) or treatment-resistant depression (Mota-Pereira et al., 2011).

Several factors influence the magnitude of success of exercise interventions. First, the exercise needs to require a larger energy expenditure to be effective in reducing depressive symptoms (Rimer et al., 2012). For instance, adult patients who completed three to five sessions per week of the more intense — aerobic — exercise for 12 weeks showed higher improvement than those in the low dose of three to five times per week of flexibility (less intense) exercise (Dunn et al., 2005). Second, the type of exercise also plays a role in intervention effectiveness. For example, completing only aerobic exercise (the type of exercise that increases the heart rate) is slightly less effective than combining aerobic exercise with resistance training (involving muscle toning, Rimer et al., 2012). Finally, exercising individually or in a group shows comparable benefits for patients suffering from depression. However, and somewhat counterintuitively, exercising alone as opposed to in groups may contribute to higher compliance (Stanton & Reaburn, 2014). Two separate studies testing individual exercise sessions (Chu et al., 2009) or both individual and group sessions (Mota-Pereira et al., 2011) showed higher compliance than other studies including only group exercise sessions. Thus, the exercise programs that are most effective in improving depressive symptoms are those that have higher intensity, involve both aerobic and resistance exercise, and are practiced either individually, or together with a group component.

Heterogeneity of depression

Despite there being many types of evidence-based treatment for depression, positive outcomes take years to achieve, and treatment is often unsuccessful (Gaynes et al., 2009). This

may be in part due to the mismatch between the treatment selected and the individual patient case. Depression is highly heterogenous, presents with many symptoms, and can manifest through vastly different clusters of psychopathology, despite being considered a unified syndrome. Using the nine symptoms given in the DSM-V for diagnosing depression, one can *theoretically* have 16 400 different unique patient symptom profiles that are all diagnosed with depression (Fried & Nesse, 2015). In practice, a study based on a large-scale project determining the heterogeneity of depression found at least 1030 unique profiles among depressive patients (Fried & Nesse, 2015). The most common symptom profile included only 1.8% of the 3703 study sample participants (Fried & Nesse, 2015). This extreme heterogeneity translates into treatment difficulties, with different profiles showing different levels of response to pharmacological treatment. As a result, only a third of patients achieve remission from the first antidepressant attempt (John Rush et al., 2006), and the process of treating often involves a lengthy trial and error process (Trivedi, 2016).

Precision approaches

Precision treatments offer a solution to the problem of heterogeneity in depression. For instance, a novel "fast-fail" approach focuses on determining the patient's dopamine response levels to receiving rewards and providing them with treatment inhibiting of particular opioid receptors (Krystal et al., 2020). Further, machine learning is also being used to predict treatment effectiveness based on patients' symptom characteristics. In a prospective study, Rajpurkar and colleagues (2020) collected treatment response to specific antidepressants from 518 patients suffering from Major Depressive Disorder. They were then able to predict treatment response on 12 out of 21 symptoms with over 80% accuracy based on patients' pre-treatment symptoms and EEG features. Finally, the choice of psychotherapy, in turn, can also depend on predictive

behavioural markers like parental alcohol abuse (van Bronswijk et al., 2019), or more environmental factors, like gender, employment status, and quality of life (Huibers et al., 2015). Once implemented, these predictors have the potential to improve the effectiveness of the chosen therapies, be it pharmacological, behavioural, or cognitive; they also may reduce the duration of trial-and-error period drastically, thus reducing the overall disability and treatment period for patients.

Role of expectations in treatment of depression

One caveat of introducing such a tailored approach to treatment may be boosting patient expectations and thus the observed better effectiveness of the treatment. The placebo effect is responsible for a large portion of patient improvement from depression treatments (Wampold et al., 2005); antidepressants often do not outperform placebos in clinical trials (Arroll et al., 2016; Davidson, 2010; Ioannidis, 2008). In one of the earliest meta-analyses on the effects of antidepressant medication on depression, Kirsch and Saperstein (1998) calculated the effect size for antidepressant medications across 19 clinical trials and 2318 patients. They determined that, across different types of antidepressant- and non-antidepressant medication, effect from the placebo controls was 75% of the size of the active drug. A follow-up meta-analysis with Food and Drug Administration data from six most popular antidepressants found placebo effect to account for 80% of the effect, with patients on medication improving by only two extra points on the Hamilton Depression Scale (Kirsch et al., 2002). Later meta-analyses found similar results (Kirsch et al., 2008; Rief et al., 2009), and some suggested that antidepressant treatments do not meet criteria for providing clinically significant improvement except for patients with extreme cases of severe depression (Kirsch et al., 2008). Although the debate on the degree of antidepressant effectiveness and the role of placebo effect continues (see Fountoulakis & Rgen

Möller, 2012; Hieronymus et al., 2018; and Horder et al., 2011), there is little doubt that a substantial part of the antidepressant therapeutic effect is due to the placebo response.

Placebo effects are also present in psychotherapy, with some researchers considering psychotherapy's effectiveness due entirely to the psychological factors such as patient expectations (Kirsch, 2005). Kirsch (2005) argues that the contextual factors one needs to control for in medical trials, where the goal is to isolate physical properties of the drug, are at the core of the psychotherapy treatments. He states:

> "Most psychotherapies do not have physically active properties. Their substance is words, but it is not the sound of the words having an effect. Rather, it is their meaning. Moerman and Jonas (2002) have defined the placebo effect as a patient's response to the meaning of a treatment. In this sense, most psychotherapy is a placebo by definition; it is an effective treatment because of its psychological properties rather than its physical properties."

Further, a growing literature focuses on the "common factors" of psychotherapy, or the non-specific ingredients that are present across different approaches and likely substantially drives its effectiveness (Cuijpers et al., 2019; Laska et al., 2014; Rosenzweig, 1936). Factors like therapist empathy, patient expectations, and therapeutic alliance are hypothesized to strongly contribute to improvements often seen in clinical trials (Wampold, 2015). Whether psychotherapy indeed has no specific ingredients and is a potent placebo rather than an active treatment, it is still reliably effective in reducing depressive symptoms.

Finally, even exercise treatment does not seem to be immune from the effects of patient expectancies, although comparatively fewer studies have explored the placebo effects of exercise programs. In one meta-analysis, nine studies including 661 participants were selected based on testing the effectiveness of exercise training programs against placebo training (i.e., flexibility exercises) on depressive symptom outcomes (Lindheimer et al., 2015). The effect size of the placebo response amounted to less than a half (Cohen's d = .20) of the effect of the treatment of following an exercise program (Cohen's d = .37). Therefore, even the more physical types of treatment such as exercise can benefit from heightened patient expectations in providing better treatment outcomes.

Aims and hypothesis

In this study, we aimed to conceptually extend the promising but non-significant findings from the previous study in the context of depression. We also chose an active intervention of physical exercise as the treatment to tailor. We varied the therapeutic outcome and type of suggestions to generalize our findings to the broader context of precision medicine. Given the same caveats of working with patients, we focused on a sub-clinical population of young adults with depressive symptoms but no clinical history. There were three hypotheses. First, we expected physical exercise to be effective in reducing depression and anxiety symptoms in a sub-clinical group of young adults. Second, we hypothesized that providing a treatment seemingly tailored to one's individual symptoms by a highly effective algorithm would make the intervention more effective in reducing depressive and anxiety symptoms. Third, we expected participants receiving a "tailored" intervention to show higher compliance.

Methods

Participants

Inclusion and exclusion criteria

Participants were invited to participate in the study if they fulfilled several inclusion criteria. We selected those aged between 18 and 35, with normal vision, without prior psychiatric or neurological diagnosis (including depression), and no physical conditions impeding exercise. We excluded participants that had a clinical history of depression or were already engaging in regular exercise (defined as at least 3 times a week, for at least 1 hour) to reduce confounding factors. Importantly, to qualify for the study, participants also first completed the Beck Depression Inventory-II questionnaire (BDI-II) and had to score 10 or higher. This kept them within the bounds of subclinical symptoms as defined by the BDI-II threshold yet allowed for room to improve.

Sample characteristics

We recruited 54 young adults from McGill and the local community. We excluded 14 participants from the final analyses: 6 participants did not complete the entire study, 4 did not complete the study on time (they completed the final questionnaires later than 16 weeks after the start of the intervention), 2 guessed the personalisation component of the study, and 2 started following an exercise program during the first week of monitoring. The final sample included 40 young adults ($n_{control}$ = 21). Participants were on average 23.48 years old (SD = 4.29) and predominantly female (31 women); participants were mostly Caucasian (43%) or Asian (43%).

Design

The study was approved by the McGill Review Ethics Board-II (#20-11-007). In this mixed-design experiment, the participants were invited for a 3-week study exploring the effectiveness of different online interventions for depressive symptoms (see Figure 5 for full study design). During the first week participants reported the dependent measures of mood, anxiety, and depression, to provide a baseline no-treatment comparison and eliminate the confound of surreptitious improvement due to participating in the study. Seven days later, they completed the same questionnaires at baseline before being randomly assigned to either a control or experimental condition. Both groups then completed further personality and health questionnaires. For the experimental group, the researcher interpreted these questionnaires as necessary to tailor the intervention to participants' individual profiles, whereas the control group believed them to be just additional personality correlates. Both groups then received the physical exercise intervention, which they followed for two weeks, completing 6 sessions of approximately 45 minutes each (Figure 6).

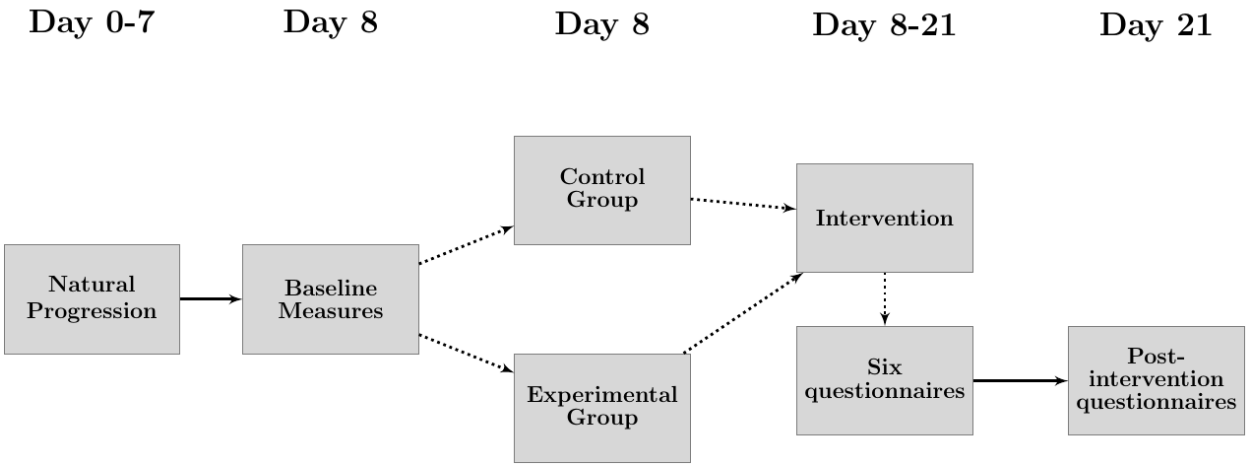


Figure 5. Study 2 design.

INTERVENTION: EXERCISE PROGRAM

Warm-up	5 minutes of walking **OR** climbing stairs in a relaxed manner

Muscle Training	Number of repetitions **OR** Time spent on exercise	Number of sets (number of times you need to complete the repetitions or time spent on exercise)
Lunge	**15 repetitions each side**	**4 sets**
Plank	**30 seconds**	**4 sets**
Side plank	**30 seconds each side**	**4 sets**
Pushup	**15 repetitions**	**4 sets**
Squat	**15 repetitions**	**4 sets**
Towel row	**15 repetitions**	**4 sets**
Back bridge	**15 repetitions**	**4 sets**

Cardiovascular Training	15 minutes of walking outside (should feel warm and slightly out of breath)

Figure 6. Exercise program intervention provided to participants. Those in the experimental group received the intervention marked with their name, participant number, and date and time of administration (not shown). Those in the control condition received the intervention as demonstrated.

Intervention rationale

We chose the physical exercise program as our intervention for two reasons. First, it is a flexible intervention that can be followed without professional supervision in a variety of settings (e.g., at home, outside, in a gym) with similar effectiveness. Indeed, studies testing the effectiveness of exercise programs often use walking outside, exercises at home, and sessions at the gym as effective interventions (Lindheimer et al., 2015). As a result, this intervention lent itself well to the constraints of running the study during the coronavirus pandemic and allowed us to use a real intervention instead of a placebo. Recent studies suggest that placebos

administered remotely have a lower effectiveness (Kirsch et al., 2021); using remote placebo antidepressants had the potential to artificially deflate the effect.

Second, exercise programs show the lowest levels of placebo effects among the standard evidence-based treatments for depression at approximately half of the effect (Lindheimer et al., 2015) versus 80% placebo for antidepressant medication (Kirsch et al., 2002). Placebo response in psychotherapy is unclear due to lack of clarity on parsing out of the placebo effect (Kirsch, 2005). Choosing exercise as the intervention offered a balance of a widely used, flexible, and evidence-based intervention with, theoretically, less potential for ceiling effects.

Duration rationale

Further, we chose the length of the intervention to balance the demonstration of real benefit and the feasibility of the study. BDI-II—the main measure of depressive symptoms and therefore one of the two main dependent variables in the study—measures the symptom intensity over the previous two weeks. As a result, we chose our participants to follow the intervention for 14 days. Although brief, the length of such an intervention is adequate: one meta-analysis found studies showing effectiveness of exercise on depression to vary from 10 days to 16 weeks (Cooney et al., 2013). Another found no moderating effect of the length of the exercise intervention onto the effectiveness in reducing depressive symptoms (Schuch et al., 2016).

Measures

Beck Depression Inventory-II (BDI-II)

The BDI assesses the severity of depressive symptoms over the previous two weeks (Beck, 1948). The questionnaire has 21 items with scores ranging from 0 to 63, with 14 being the

cut-off for mild clinical depression. Each item measures a specific area (e.g., sadness) and has answers varying from 0 to 3, for example, “I do not feel sad” (0 points) to “I am so sad or unhappy that I can’t stand it” (3 points). The scale’s internal consistency is high ($\alpha = .93$).

International Positive and Negative Affect Scale X (I-PANAS-X)

The PANAS measures positive and negative affect (Thompson, 2007). Participants rate the intensity of affect based on a total of 10 items (e.g., Interested, Hostile) on 5-point scales ranging from 1 (Never) to 5 (Always). Total scores on positive and negative affect each range from 10 to 50. The scale had acceptable reliability ($\alpha = .75$ for positive affect and $\alpha = .76$ for negative).

Hospital Anxiety and Depression Scale (HADS)

The HADS is a brief questionnaire that assesses symptoms of depression and anxiety over the past week in a hospital setting (Zigmond & Snaith, 1983). Participants answer items such as “I feel tense or ’wound up’” on a scale from 0 (Not at all) to 3 (Most of the time). The scale includes two different scores, each ranging from 0 to 21 with cut-off of 11 for definite cases of depression or anxiety. It has a good reliability ($\alpha = .80$).

Credibility/Expectancy Questionnaire (CEQ)

The CEQ is a 6-item questionnaire measuring thoughts and feelings about credibility and effectiveness of a given treatment (Devilly & Borkovec, 2000). The questionnaire is composed of two subscales for thoughts (items 1-3) and feelings (items 4-6) and includes multiple ratings. Four items on treatment expectancy are measured on a scale from 1 (Not at All) to 9 (Very)the remaining two items focusing on expected improvement are measured from 0% to 100%.

Thought subscale score ranges from 3 to 27, and feelings score ranges from 1 to 29. The questionnaire has good reliability (α = .86).

Procedure

Recruitment

We recruited participants from both the McGill University community, local community, and McGill Psychology Participant Pool. Those interested in participating in the study filled out the pre-screening measure of BDI-II and qualified based on all exclusion criteria.

Baseline monitoring

During the initial Zoom meeting participants completed a baseline (T_1) set of questionnaires: BDI-II, PANAS, and HADS. Then, participants completed a subset (PANAS and HADS) twice more as a baseline week assessment. This was to mimic the rest of the procedure during the active intervention and control for positive effects of being in a study. At the end of the baseline week of monitoring, the participants were randomly assigned either to the experimental or the control condition.

Personalized intervention condition

On day 8, participants took part in another Zoom meeting where they filled out the same baseline questionnaires (BDI, PANAS, HADS). The experimenter then described the algorithm and stated that she would use it to determine the best intervention for the participant based on their profile. The algorithm was described as developed by the UK Biobank and trained on hundreds of thousands of biological and behavioural data and effective in predicting optimal treatment based on clinical profile (see Appendix D for the full script). The experimenter

emphasized the importance of gathering this information and asked participants to sign an additional consent form agreeing to use the algorithm (see Appendix E for the consent form). Once agreed, the participants completed several filler questionnaires of general health and sleep profiles. They then received their physical exercise intervention in the email, complete with their name, participant ID, and the date of reception. The exercise program was identical for all participants across both groups and included a warm-up (5 minutes), a muscle training section (25 – 30 minutes), and an aerobic training section (15 minutes, Figure 6). The experimenter walked participants through each step of the program and encouraged them to follow it three times a week for the next two weeks. If participants complete at least five out of six sessions of the intervention, they were offered a bonus of $20 in addition to the overall study compensation.

Control condition

Those in the control condition completed exactly the same procedure as the experimental condition with one exception: the experimenter explained the additional questionnaires as covariate variables needed to match the sample. The participant then received a consent form to sign to confirm they understood the confidentiality rules around providing data online, and once signed, the link for the same questionnaires to complete as in the experimental condition (see Appendix E for the consent form for the control group). The rest of the procedure matched the experimental condition.

Expectations

Lastly, all participants completed the Credibility/Expectancy Questionnaire to determine their baseline expectations of treatment effectiveness.

Outcomes

Both groups followed the intervention for two weeks and six sessions, receiving email notifications to complete the HADS questionnaire each week, and the PANAS questionnaire before each session. To assess compliance, we asked participants *before* each session whether they completed the previous round of exercises, and, if yes, to rate the percentage of exercises completed from 0% to 100%. At the end of the third week, participants completed the post-intervention questionnaires (BDI-II, PANAS, HADS) as well as their overall experience with the study. We also probed them for suspicion about the true nature on the study before debriefing them (Nichols & Edlund, 2015).

Analysis plan

All confirmatory analyses of the study were pre-registered online (https://osf.io/nqzj7). We had two hypotheses. First, we expected that participants receiving an ostensibly personalized intervention would show larger improvements on their scores of depression and anxiety. To test this hypothesis, we ran two separate mixed-effects regression tests on the outcomes (depressive and anxiety symptoms), given the condition (tailored or control), time (pre- or post-intervention) and the interaction between the two variables with the participant as a random factor. We only tested the interaction for significance, using Type I error rate of 0.05 and one-tailed tests.

Second, we expected that believing that the intervention is individually tailored to one's profile may improve compliance. We tested this hypothesis using an independent samples one-tailed t-test at 0.05 level of significance.

Results

Passive monitoring

During the first week, participants showed no reductions in symptoms on any measures, suggesting that simply being enrolled in a study or answering questionnaires did not lead to symptom reduction (see Table 1 for statistical test results for all measures).

Table 1. Comparison of depression, anxiety, and mood scores before and after the first week of monitoring. Groups showed no improvement from simply being enrolled in the study.

Measure	t-statistic	df	95% CI	p-value
BDI-II	-0.70	39	$-2.03, 4.17$	$.49$
HADS-D	0.44	39	$-1.46, 2.28$	.66
HADS-A	1.88	39	$-0.13, 3.24$	.07
Positive Mood	-1.34	39	$-1.14, 0.21$	.19
Negative Mood	0.55	39	$-1.31, 2.30$	.58

Confirmatory findings

Depression

Participants in both groups showed similar baseline depression scores. The average depression baseline score at the start of the intervention was 27.3 points [22.96, 31.78] in the experimental group and 27.5 points [24.15, 30.80] in the control group on the BDI-II scale (14

being the cut-off for mild depressive symptoms). They also scored 9.58 points [7.64, 10.27] in the experimental group and 8.95 [8.46, 10.70] in the control group on the HADS depression subscale (ranging from 0 to 21).

Over the course of the two-week intervention, both groups showed similar declines on symptoms of depression, with no effects of expectation manipulation (standardized $b_{\text{BDI-II}}$ = - 0.11 [-0.64, 0.42], p = .33, $b_{\text{HADS-D}}$ = 0.03 [-0.55, 0.50], p = .46). Table 2 shows the full regression model coefficients and Figure 7A & 7B demonstrates the graphs of changes for confirmatory analyses.

Anxiety

Overall, we found no effect of enhanced expectations on anxiety symptom reduction ($b_{\text{HADS-A}}$ = -0.23 [-0.68, 0.24] p = .16). Participants in the experimental group decreased by 3.90 points [2.63, 5.17], and those in the control group by 2.84 points [1.56, 4.11] (Figure 7C).

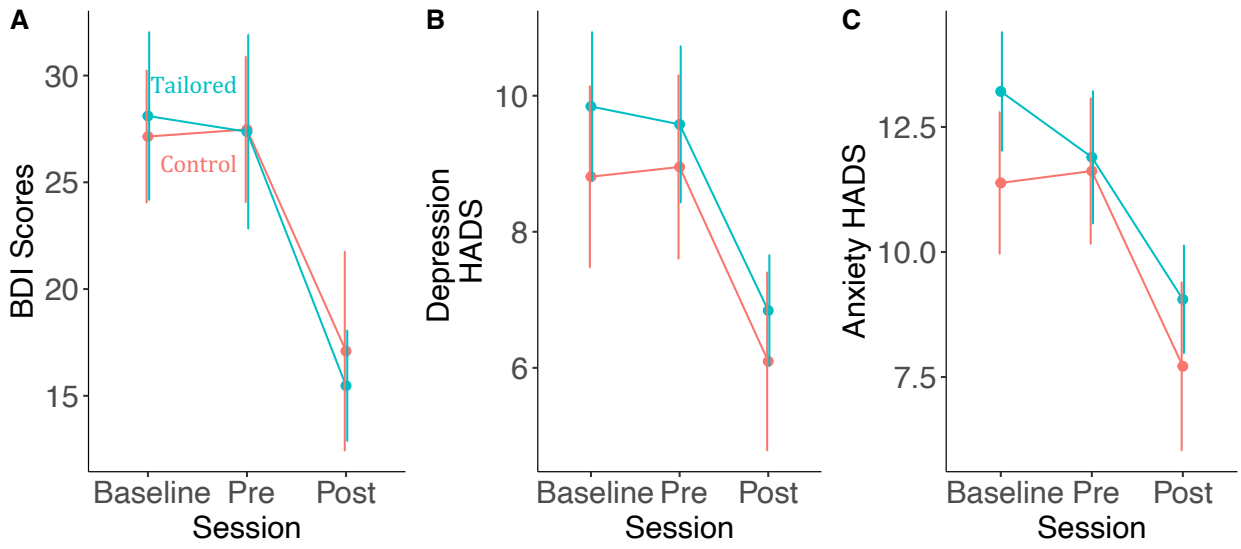


Figure 7. Effects of the intervention and manipulation of expectation effectiveness on depression scores on BDI-II (A) and HADS-D scale (B), as well as anxiety (C). Error bars represent 95% CIs.

Compliance

Both groups showed similar levels of compliance with the intervention (*b* = - 0.1 [-0.75, 0.55], *p* = .76). Participants in both groups completed on average 80% of the exercises per session [67.32, 92.68] and 5.4 out 6 sessions [4.7, 6.1] (see Figure 8).

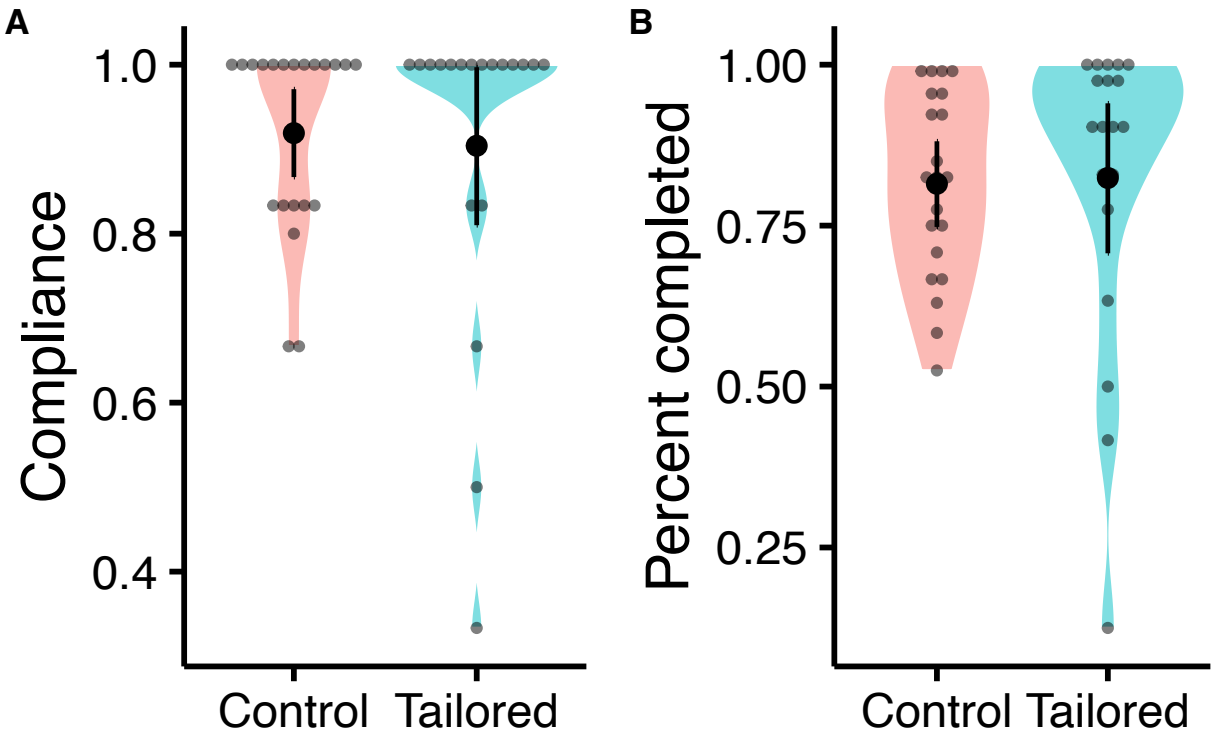


Figure 8. Compliance ratings of sessions completed (A) and percent exercise per session completed (B). Error bars represent 95% CIs.

Exploratory findings

General effectiveness of exercise

Exercise was effective in reducing depressive symptoms as measured by the BDI-II and HADS-D scales. Participants showed large improvements on depressive symptoms after the two-week intervention (standardized $b_{\text{BDI-II}}$ = -0.78 [-1.14, -0.41], $p < .001$, $b_{\text{HADS-D}}$ = - 0.73 [- 1.09, -0.37], $p < .001$). The experimental group showed an average reduction of 11.89 points [8.18, 15.60] on the BDI-II scale, and a reduction of 2.85 points [1.68, 4.01] on the HADS-D scale. The control group's depression scores decreased by 10.38 points [6.67, 14.08] and 2.74 points [1.57, 3.91], respectively (Figure 7A & 7B).

Similarly, participants showed large reductions on anxiety symptoms following the intervention ($b_{\text{HADS-A}}$ = -0.83 [0.51, 1.15], $p <.001$). At the start of the intervention both groups showed similar anxiety scores with 11.89 points [10.60, 13.18] for the experimental and 11.62 points [10.20, 13.03] for the control group on the HADS anxiety subscale (ranging from 0 to 21). Participants in the experimental group decreased by 2.84 points [2.14, 3.55], and those in the control group by 3.9 points [2.62, 5.17] (Figure 7C).

Expectations

Participants across both groups also showed similar scores for the expectations of intervention effectiveness on the scales of thoughts (t (39) = -0.39 [-1.04, 0.26], p = .42) and feelings (t (39) = -0.32 [-0.98, 0.34], p = .67; Figure 9C).

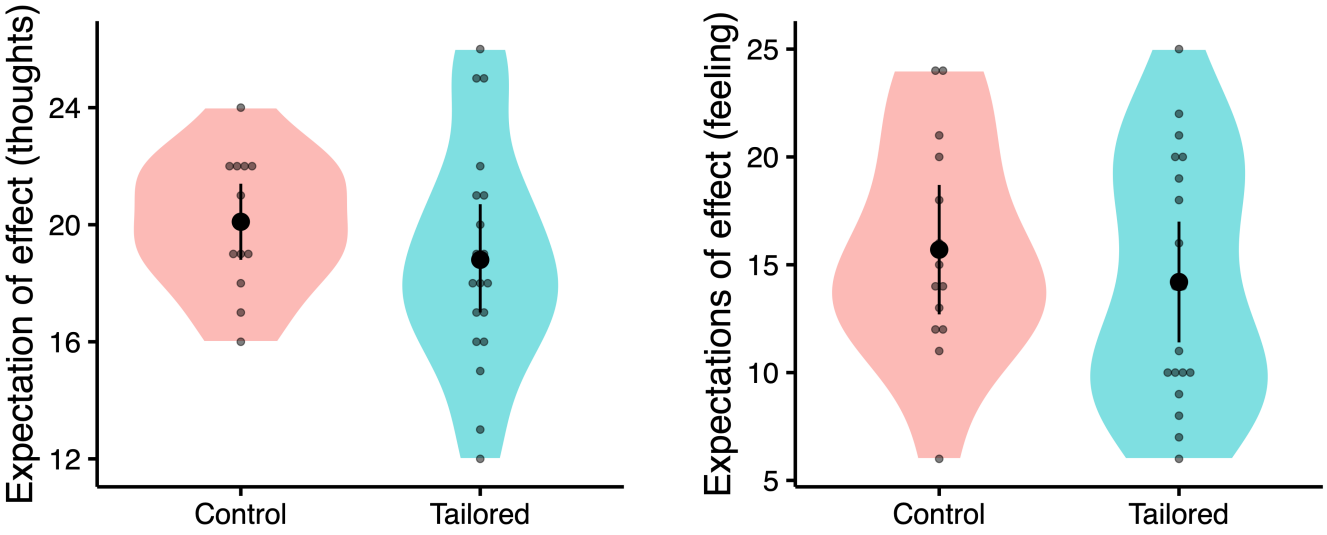


Figure 9. Expectations of intervention effectiveness in terms of thoughts (A) and feelings (B) across participants. Error bars represent 95% CIs.

Mood

Finally, participants have shown similar reductions in negative mood (control = 3.38 points [2.08, 4.68], experimental = 3.89 points [2.59, 5.19], b_{neg} = -0.12 [-0.65, 0.41], p = .33) and increases in positive mood (control = 3.43 points [2.13, 4.73], experimental = 1.89 points [0.59, 3.19], b_{pos} = -0.39 [-0.96, 0.18], p = .085) (Figure 10).

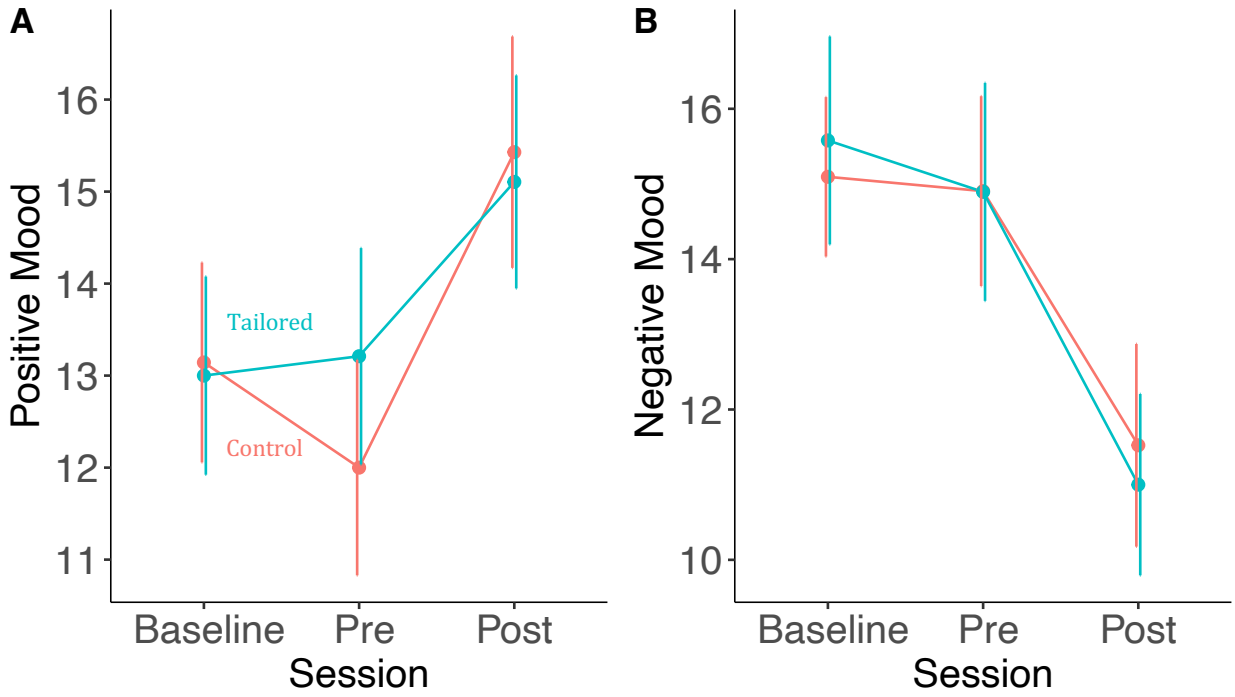


Figure 10. Effects of manipulation of expectations on improvements in positive (A) and negative (B) mood. Error bars represent 95% CIs.

Table 2. Regression model coefficients for confirmatory and exploratory findings. Interactions are highlighted in bold; statistically significant results are italicized.

Type	**Outcome**	**Predictor**	***b***	***CI***	***SE***	***t***	***df***	***p***
Confirma-tory	Depression scores (BDI-II)	(Intercept)	0.42		0.21			
		Condition	-0.01		0.30			
		Time	*-0.78*	*-1.14, -0.41*	*0.18*	*- 8.7*	*38*	*<.001*
		Interaction	**-0.11**	**-0.64, 0.42**	**0.26**	**-0.88**	**38**	**.33**
	Depression scores (HADS-D)	(Intercept)	0.28		0.21			
		Condition	0.16		0.32			
		Time	*-0.73*	*- 1.09, -0.37*	*0.18*	*-7.98*	*38*	*<.001*
		Interaction	**0.03**	**-0.55, 0.50**	**0.26**	**0.22**	**38**	**.46**
	Anxiety scores (HADS-A)	(Intercept)	0.33		**0.20**			
		Condition	0.05		0.30			
		Time	*-0.83*	*0.51, 1.15*	*0.16*	*- 10.6*	*38*	*<.001*
		Interaction	**-0.23**	**-0.68, 0.24**	**0.23**	**-1.98**	**38**	**.16**
	Compliance	(Intercept)	-0.05		**0.22**			
		Interaction	**-0.10**	**-0.75, 0.55**	**0.32**	**-0.31**	**38**	**.76**
		(Intercept)	-0.49		0.20			
		Condition	-0.31		0.30			
Explora-tory	Positive Mood	*Time*	*0.87*	*0.30, 1.44*	*0.28*	*9.06*	*38*	*<.001*
		Interaction	**-0.39**	**-0.96, 0.18**	**0.28**	**- 2.8**	**38**	**.085**

	(Intercept)	0.41		0.21			
	Condition	-0.01		0.30			
Negative Mood	*Time*	*-0.76*	*-1.12, -0.39*	*0.18*	*- 8.6*	*38*	*<.001*
	Interaction	**-0.12**	**0.65, 0.41**	**0.26**	**- 0.9**	**38**	**.33**

Discussion

We tested whether the expectations of interpreting an intervention of physical exercise as individually tailored to one's clinical profile affects reductions in symptoms of depression, anxiety, and intervention compliance. The exercise intervention was indeed effective in reducing symptoms even when presented for a brief duration of 14 days. However, we found no support for the two primary hypotheses about the role of personalisation expectations on superior treatment effectiveness.

Limitations

Our null results could have been due to several methodological limitations. The first limitation consisted in choosing physical exercise as the intervention, which may have affected participants' expectations of the enhanced effectiveness of algorithm's choice. Indeed, participants showed similar expectations of exercise effectiveness across both groups, with a trend towards lower expectations in the experimental group. This could be due to disappointment from receiving exercise as opposed to a more salient intervention like psychotherapy or antidepressant medications. In addition, exercise requires substantial motivation and effort to be effective, as opposed to more passive interventions like medication or weekly therapist visits. Receiving exercise instead may have reduced their expectations of the overall credibility of the algorithm that "chose" it, and the resulting "superior" helpfulness of the exercise for their

specific case. It may also have contradicted their previous experience, as they may have likely already used exercise to manage their symptoms prior to the study with various degrees of success.

In addition, participants may not have believed in the higher effectiveness of exercise as tailored treatment due to its "low-resource" nature. Standard treatments for depression are often resource-intensive: they are costly, last over a substantial period of time, and involve trained professionals. This likely enhances the expectations of their effectiveness. Indeed, researchers demonstrated more expensive treatments to increase therapeutic expectations (Waber et al., 2008) and others hypothesised the positive effect of professional attention on outcomes (Kaptchuk, 2002; Olson et al., 2021). With many exercise programs the inverse is true. Physical exercise programs are widely and freely available online and often are *not* tailored to the individual's needs. To get a tailored exercise program one would need a physical assessment and a visit with a professional like a kinesiologist or a physiotherapist. In our study, the exercise program looked similar to those on the internet and lacked the appearance of professional involvement, despite having been professionally developed by a kinesiologist. Participants may have therefore been sceptical about its promise for higher effectiveness despite the clinical assessment and the presence of the algorithm, thus showing similar symptom improvement as the control group.

Another methodological limitation was providing participants with algorithm-based treatment tailoring, as opposed to a physiology-based one as in Study I. Due to the COVID-19 pandemic we were unable to collect any physical samples and thus chose an algorithm-based tailoring. Indeed, the public is favourable of artificial intelligence approaches and holds positive expectancies about their ability to enable medical and technological advances (Kerr et al., 2020).

However, the presence of an algorithm on its own or with a simple clinical assessment may not have been potent enough to enhance expectations. Future studies could include AI-based prediction that uses physiological measures such as brain scans and genetic markers to strengthen expectations and better mimic current practice (Lee et al., 2018).

Strengths

Despite the null results on the effects of expectations of treatment tailoring, our study found a large effect (*Cohen's d* = 0.73 & 0.78) of physical exercise on depressive symptoms. This is in line with previous meta-analyses reporting the largest effect sizes of exercise in the literature (*d* = 1.11, Schuch et al., 2016). More surprisingly, our effects were detectable after only 14 days of exercise. In contrast, the shortest study included in the meta-analysis by Schuch and colleagues (2016) is over 3 weeks, with the average study length standing at 10.3 weeks. Although the authors found no moderating effects of length of the intervention in the longer trials, our study demonstrates exercise is highly effective in reducing depressive symptoms even over a very short period and for sub-clinical populations.

The intervention might have also been particularly effective due to the specific context of the coronavirus pandemic. The global crisis has brought various restrictions for most of the population and led to a more sedentary lifestyle (Teychenne et al., 2010). It is likely that participants' increase in sedentary time may have contributed to the increases in depressive symptoms, and that a physical exercise intervention was particularly effective in reducing sedentarity-induced depression. Indeed, increases in sedentary time may be associated with increased risk of depressive symptoms (Teychenne et al., 2010; Zhai et al., 2015). Future studies

should explore whether level of baseline sedentary lifestyle moderates the effectiveness of physical exercise interventions on depression.

General discussion

Summary of findings

The field of precision medicine is growing and suggests tailored approaches to be superior to the standard options. Although there are some early successes, it is still unknown whether a portion of the superior effectiveness of tailored treatments is due to the therapeutic effect of patients' positive expectations. The overarching goal of this thesis was to determine the role of expectations associated with treatment tailoring in the general medical context and in the treatment of depression. In the feasibility Study 1, we found a promising but non-significant trend: increased reductions in experimental pain intensity and unpleasantness in healthy participants. In the online Study 2, we corroborated previous findings of positive effects of exercise on depressive and anxiety symptoms. However, we found no effect of expectations associated with personalising the intervention on improvement in depressive symptoms on subclinical population of young adults. This was likely due to methodological constraints. We next discuss the overarching limitations of the present work.

Limitations

Healthy population

The major limitation of the two studies was their focus on healthy, as opposed to clinical, population, thus limiting its applicability to the context of precision medicine. Individuals

currently receiving tailored treatments are primarily those suffering from severe illness like cancer. These patients likely differ in cognitive resources from their healthy counterparts. For instance, cancer patients suffer from many cognitive deficits before, during, and after cancer treatment (see Hardy et al., 2018 for a review). This in itself may impact the magnitude of the effect from positive expectations associated with targeted treatment in unforeseen ways. Additionally, patients in general (Hyland, 2011) have a stronger motivation to get better, especially those receiving tailored treatments, given that they often have recurring or treatment-resistant cancers threatening their immediate survival and quality of life (National Cancer Institute, 2021). Thus, patients in clinical contexts are likely to benefit more from positive expectations than healthy participants in lab settings (Hyland, 2011).

The mechanisms responsible for the short-term effects of expectations in experimental settings may also differ from the long-term ones in clinical populations, further limiting any conclusions. For example, placebo research shows that healthy participants in the lab experience placebo analgesia likely due to the brain's production of endogenous opioids to reduce pain (Finniss et al., 2010; Price et al., 2007). Indeed, studies of these populations and short-term pain suggest that administering naloxone—an opioid antagonist—removes placebo analgesia (Amanzio et al., 2001; Bandura et al., 1987). Real patients suffering from pain-related conditions, on the other hand, may demonstrate placebo effect through different mechanisms. In a study of 26 female Irritable Bowel Syndrome patients, researchers found no reductions of placebo effect on rectal pain after the infusion of naloxone (Vase et al., 2005), potentially suggesting a distinct mechanism of placebo action. Given the nuances seen in pain and placebo science, it becomes unreliable to map the lab-generated therapeutic effect of expectations more broadly onto the clinical context and the specific approach of precision treatments. Although

testing precision medicine patients will prove challenging, it is important to determine the psychological effects of expectations in this population directly.

Deception

In addition, both studies used deception to expressly enhance participant expectations and artificially isolate their role in better treatment response. Our results therefore likely show an inflated level of expectations associated with tailored treatment and an exaggerated magnitude of possible improvement. Additionally, the method of providing false information and feedback on test results would be infeasible to translate into clinical practice. Although deception is commonly used in experimental settings and clinical trials, deceptive treatments are considered unethical in practice due to their limiting of patient autonomy (Chan, 2014; Miller et al., 2005; Shah & Goold, 2009). Many patients also express negative attitudes towards receiving placebos or any inactive treatment without due knowledge (Fässler et al., 2011; Hull et al., 2013). While using deception to elicit placebo effects is an effective way to isolate the role of expectations in the lab, this approach limits the conclusions of both studies presented here to the specific experimental paradigm.

Future directions

Therapeutic communication

Interestingly, such elaborate deception may not be necessary to enhance expectations in precision medicine. Recent evidence across various medical conditions suggests that administering placebos openly can still bring relief to patients (for review see Charlesworth et al., 2017; von Wernsdorff et al., 2021). Further, patients are generally favourable to the use of placebos when these are presented openly and with regard for their autonomy (Fässler et al.,

2011; Hull et al., 2013). Instead of providing false genetic feedback or fake algorithms to those suffering from life-threatening diseases, it may be possible to incorporate more transparent practices from such "open-label" placebo research to enhance patient expectations in ethical ways.

For example, physicians in the field of precision medicine could focus on further enhancing patient-practitioner communication. Some experiments have suggested that warm and empathetic interactions between the doctor and the patient improve individuals' expectations, increase placebo effects, reduce side effects, and decrease clinical symptoms (Barrett et al., 2011; Howe et al., 2017, 2019). Practitioners delivering targeted treatments already involve genetic counsellors who have specific training in effective communication that some equate to psychotherapy (Austin et al., 2014). Unfortunately, these professionals often focus on providing biomedical information in favour of addressing psychosocial concerns (Meiser et al., 2008; Paul et al., 2015). Instead, they could take maximum advantage of their unique skills in therapeutic communication with the express intent of enhancing the effect of patient expectations and possibly their actual treatment response.

Going forward, genetic counsellors and physicians could also manage patient expectations directly by providing positive suggestions about the enhanced effectiveness of tailored treatments. Typically, genetic counsellors inform patients in detail on their genetic and physiological characteristics like risks and markers of disease (Kohut et al., 2019). To enhance expectations, they could frame this information as emphasizing the uniqueness of the patients' results and provide specific examples on the usefulness of these test results in the process of tailoring. Indeed, placebo studies demonstrate that verbally emphasizing the helpfulness of active drugs like morphine further increases their effect (Benedetti, Maggi, et al., 2003; Colloca et al.,

2004; Pollo et al., 2001). Practitioners could also go beyond the results themselves and explicitly emphasize the general complexity of the procedure, the advanced technology, and the use of at times invasive tests as leading to a better treatment option than a standard approach.

Ultimately, if expectations do play a substantial role in patient response to precision treatments, genetic counsellors and general practitioners involved in administration of these therapies would benefit from a broader understanding of placebo effects and techniques to enhance these in clinical practice.

Precision medicine research

Future studies should go beyond the groundwork laid here and focus on the effects of expectations in clinical settings with real precision treatments, despite the inherent practical concerns. Currently, few people are receiving individualised treatments; those that do, often do so in a context of clinical trials receiving experimental therapies. These trials, however, compare tailored treatments to standard options and often do not control for the possible change in expectations associated with therapy tailoring. Isolating the role of expectations in precision treatments could thus greatly inform the current research practices as well as the cost-benefit analysis of future tailored interventions. As these therapies enter the mainstream in the coming decades, the understanding of the role of placebo effects could provide additional practical opportunities to harness these to increase treatment effectiveness without increasing its costs. Finally, exploring the role of placebo effect in more ecologically valid settings could uncover the real magnitude of the effect of enhanced expectations and better inform the necessity of using tailored treatments in various contexts.

Conclusion

Across two studies, this thesis began to explore the effect of expectations of tailoring on treatment response. Although our findings present mixed results, they suggest a promising line of research for the field of precision medicine. As tailored approaches become widely adopted in healthcare, understanding the role of expectations and psychological factors in treatment response will become crucial in optimizing their effectiveness. If such non-medical factors do influence outcomes, leveraging them in ethical ways may potentially provide an effective method to reduce treatment cost without compromising the quality of care. Overall, patient expectations remain a largely untapped resource that may, alongside superior biochemical tailoring, improve human health.

References

Adams, S. A., & Petersen, C. (2016). Precision medicine: Opportunities, possibilities, and challenges for patients and providers. *Journal of the American Medical Informatics Association*, *23*(4), 787–790. https://doi.org/10.1093/jamia/ocv215

Agusti, A., Bel, E., Thomas, M., Vogelmeier, C., Brusselle, G., Holgate, S., Humbert, M., Jones, P., Gibson, P. G., Vestbo, J., Beasley, R., & Pavord, I. D. (2016). Treatable traits: toward precision medicine of chronic airway diseases. *European Respiratory Journal*, *47*(2), 410–419. https://doi.org/10.1183/13993003.01930-2015

Ahn, W., Bitran, A., & Lebowitz, M. (2020). Effects of genetic information on memory for severity of depressive symptoms. *PLOS ONE*, *15*(10), e0239714. https://doi.org/10.1371/journal.pone.0239714

Albert, P. R. (2015). Why is depression more prevalent in women? In *Journal of Psychiatry and Neuroscience* (Vol. 40, Issue 4, pp. 219–221). Canadian Medical Association. https://doi.org/10.1503/jpn.150205

Amanzio, M., & Benedetti, F. (1983). *Neuropharmacological Dissection of Placebo Analgesia: Expectation-Activated Opioid Systems versus Conditioning-Activated Specific Subsystems*. Fields and Price.

Amanzio, M., Pollo, A., Maggi, G., & Benedetti, F. (2001). Response variability to analgesics: A role for non-specific activation of endogenous opioids. *Pain*, *90*(3), 205–215. https://doi.org/10.1016/S0304-3959(00)00486-3

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders*. American Psychiatric Association. https://doi.org/10.1176/appi.books.9780890425596

Austin, J., Semaka, A., & Hadjipavlou, G. (2014). Conceptualizing Genetic Counseling as Psychotherapy in the Era of Genomic Medicine. *Journal of Genetic Counseling*, *23*(6), 903–909. https://doi.org/10.1007/s10897-014-9728-1

Bandura, A., O'Leary, A., Taylor, C. B., Gauthier, J., & Gossard, D. (1987). Perceived Self-Efficacy and Pain Control: Opioid and Nonopioid Mechanisms. *Journal of Personality and Social Psychology*, *53*(3), 563–571. https://doi.org/10.1037/0022-3514.53.3.563

Barrett, B., Brown, R., Rakel, D., Rabago, D., Marchand, L., Scheder, J., Mundt, M., Thomas, G., & Barlow, S. (2011). Placebo effects and the common cold: A randomized controlled trial. *Annals of Family Medicine*, *9*(4), 312–322. https://doi.org/10.1370/afm.1250

Beauchamp, M. R., Rhodes, R. E., Kreutzer, C., & Rupert, J. L. (2011). Experiential versus genetic accounts of inactivity: Implications for inactive individuals' self-efficacy beliefs and intentions to exercise. *Behavioral Medicine*, *37*(1), 8–14. https://doi.org/10.1080/08964289.2010.540263

Beecher, H. K. (1955). The powerful placebo. *Journal of the American Medical Association*, *159*(17), 1602–1606. https://doi.org/10.1001/jama.1955.02960340022006

Benedetti, F. (2014). Placebo effects: From the neurobiological paradigm to translational implications. In *Neuron* (Vol. 84, Issue 3, pp. 623–637). Cell Press. https://doi.org/10.1016/j.neuron.2014.10.023

Benedetti, F., Maggi, G., Lopiano, L., Lanotte, M., Rainero, I., Vighetti, S., & Pollo, A. (2003). Open versus hidden medical treatments: The patient's knowledge about a therapy affects the therapy outcome. *Prevention & Treatment*, *6*(1). https://doi.org/10.1037/1522-3736.6.1.61a

Benedetti, F., Pollo, A., & Colloca, L. (2007). *Opioid-Mediated Placebo Responses Boost Pain Endurance and Physical Performance: Is It Doping in Sport Competitions?* https://doi.org/10.1523/JNEUROSCI.3330-07.2007

Benedetti, F., Pollo, A., Lopiano, L., Lanotte, M., Vighetti, S., & Rainero, I. (2003). *Conscious Expectation and Unconscious Conditioning in Analgesic, Motor, and Hormonal Placebo/Nocebo Responses*.

Bernstein, M. H., Locher, C., Kube, T., Buergler, S., Stewart-Ferrer, S., & Blease, C. (2020). Putting the 'Art' Into the 'Art of Medicine': The Under-Explored Role of Artifacts in Placebo Studies. *Frontiers in Psychology*, *11*, 1354. https://doi.org/10.3389/fpsyg.2020.01354

Blasini, M., Peiris, N., Wright, T., & Colloca, L. (2018). The Role of Patient–Practitioner Relationships in Placebo and Nocebo Phenomena. In *International Review of Neurobiology* (Vol. 139, pp. 211–231). Academic Press Inc. https://doi.org/10.1016/bs.irn.2018.07.033

Blumenthal, J. A., Babyak, M. A., Doraiswamy, P. M., Watkins, L., Hoffman, B. M., Barbour, K. A., Herman, S., Craighead, W. E., Brosse, A. L., Waugh, R., Hinderliter, A., & Sherwood, A. (2007). Exercise and pharmacotherapy in the treatment of major depressive disorder. *Psychosomatic Medicine*, *69*(7), 587–596. https://doi.org/10.1097/PSY.0b013e318148c19a

Blumenthal, J. A., Babyak, M. A., Moore, K. A., Craighead, ; W Edward, Herman, S., Khatri, P., Waugh, R., Napolitano, M. A., Leslie, M. ;, Forman, M., Appelbaum, M., Doraiswamy, ; P Murali, & Krishnan, ; K Ranga. (1999). Effects of Exercise Training on Older Patients With Major Depression. *Archives Internal Medicine*, *159*(19), 2349–2356. www.archinternmed.com

Blythe, J. S., Peerdeman, K. J., Veldhuijzen, D. S., van Laarhoven, A. I. M., & Evers, A. W. M. (2019). Placebo and nocebo effects on itch: a review of experimental methods. *Itch*, *4*(3), e27–e27. https://doi.org/10.1097/itx.0000000000000027

Boehm, K., Berger, B., Weger, U., & Heusser, P. (2017). Does the model of additive effect in placebo research still hold true? A narrative review. *Journal of the Royal Society of Medicine Open*, *8*(3). https://doi.org/10.1177/2054270416681434

Button, K. S., Ioannidis, J. P. A., Mokrysz, C., Nosek, B. A., Flint, J., Robinson, E. S. J., & Munafò, M. R. (2013). Power failure: Why small sample size undermines the reliability of neuroscience. *Nature Reviews Neuroscience*, *14*(5), 365–376. https://doi.org/10.1038/nrn3475

Bzdok, D., & Meyer-Lindenberg, A. (2018). Machine Learning for Precision Psychiatry: Opportunities and Challenges. In *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* (Vol. 3, Issue 3, pp. 223–230). Elsevier Inc. https://doi.org/10.1016/j.bpsc.2017.11.007

Cai, H., Zou, X., Feng, Y., Liu, Y., & Jing, Y. (2018). Increasing Need for Uniqueness in Contemporary China: Empirical Evidence. *Frontiers in Psychology*, *9*(MAY), 554. https://doi.org/10.3389/fpsyg.2018.00554

Cao, B., Cho, R. Y., Chen, D., Xiu, M., Wang, L., Soares, J. C., & Zhang, X. Y. (2020). Treatment response prediction and individualized identification of first-episode drug-naïve schizophrenia using brain functional connectivity. *Molecular Psychiatry*, *25*(4), 906–913. https://doi.org/10.1038/s41380-018-0106-5

Cartwright, N. (2007). Are RCTs the gold standard? *BioSocieties*, *2*(1), 11–20. https://doi.org/10.1017/S1745855207005029

Chan, T. E. (2014). Regulating the placebo effect in clinical practice. *Medical Law Review*, *23*(1), 1–26. https://doi.org/10.1093/medlaw/fwu026

Charlesworth, J. E. G., Petkovic, G., Kelley, J. M., Hunter, M., Onakpoya, I., Roberts, N., Miller, F. G., & Howick, J. (2017). Effects of placebos without deception compared with no treatment: A systematic review and meta-analysis. *Journal of Evidence-Based Medicine*, *10*(2), 97–107. https://doi.org/10.1111/jebm.12251

Chu, I. H., Buckworth, J., Kirby, T. E., & Emery, C. F. (2009). Effect of exercise intensity on depressive symptoms in women. *Mental Health and Physical Activity*, *2*(1), 37–43. https://doi.org/10.1016/j.mhpa.2009.01.001

Cipriani, A., Furukawa, T. A., Salanti, G., Chaimani, A., Atkinson, L. Z., Ogawa, Y., Leucht, S., Ruhe, H. G., Turner, E. H., Higgins, J. P. T., Egger, M., Takeshima, N., Hayasaka, Y., Imai, H., Shinohara, K., Tajika, A., Ioannidis, J. P. A., & Geddes, J. R. (2018). Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *The Lancet*, *391*(10128), 1357–1366. https://doi.org/10.1016/S0140-6736(17)32802-7

Colloca, L., & Barsky, A. J. (2020). Placebo and Nocebo Effects. *New England Journal of Medicine*, *382*(6), 554–561. https://doi.org/10.1056/NEJMra1907805

Colloca, L., & Benedetti, F. (2006). How prior experience shapes placebo analgesia. *Pain*, *124*(1–2), 126–133. https://doi.org/10.1016/j.pain.2006.04.005

Colloca, L., & Benedetti, F. (2009). Placebo analgesia induced by social observational learning. *Pain*, *144*(1), 28–34. https://doi.org/10.1016/j.pain.2009.01.033

Colloca, L., Lopiano, L., Lanotte, M., & Benedetti, F. (2004). Overt versus covert treatment for pain, anxiety, and Parkinson's disease. In *Lancet Neurology* (Vol. 3, Issue 11, pp. 679–684). Lancet Publishing Group. https://doi.org/10.1016/S1474-4422(04)00908-1

Cooney, G., Dwan, K., & Mead, G. (2014). Exercise for depression. *JAMA - Journal of the American Medical Association*, *311*(23), 2432–2433.

https://doi.org/10.1001/jama.2014.4930

Cooney, G. M., Dwan, K., Greig, C. A., Lawlor, D. A., Rimer, J., Waugh, F. R., McMurdo, M., & Mead, G. E. (2013). Exercise for depression: Some benefits but better trials are needed. *Cochrane Reviews*, *34*(11), 1203. https://doi.org/10.1002/14651858.CD004366.pub6

Corcoran, R. B. (2020). Liquid biopsy versus tumor biopsy for clinical-trial recruitment. In *Nature Medicine* (Vol. 26, Issue 12, pp. 1815–1816). Nature Research. https://doi.org/10.1038/s41591-020-01169-6

Craft, L. L., & Perna, F. M. (2004). The Benefits of Exercise for the Clinically Depressed. *The Primary Care Companion to The Journal of Clinical Psychiatry*, *06*(03), 104–111. https://doi.org/10.4088/pcc.v06n0301

Cuijpers, P., De Wit, L., Weitz, E., Andersson, G., & Huibers, M. J. H. (2015). Combined Treatment of Adult Depression. In *Journal of Evidence-Based Psychotherapies* (Vol. 15, Issue 2). www.evidencebasedpsychotherapies.org

Cuijpers, P., Reijnders, M., & Huibers, M. J. H. (2019). The Role of Common Factors in Psychotherapy Outcomes. In *Annual Review of Clinical Psychology* (Vol. 15, pp. 207–231). Annual Reviews Inc. https://doi.org/10.1146/annurev-clinpsy-050718-095424

Cuijpers, P., Sijbrandij, M., Koole, S. L., Andersson, G., Beekman, A. T., & Reynolds, C. F. (2014). Adding psychotherapy to antidepressant medication in depression and anxiety disorders: A meta-analysis. *World Psychiatry*, *13*(1), 56–67. https://doi.org/10.1002/wps.20089

Cuthbert, B. N., & Insel, T. R. (2013). Toward the future of psychiatric diagnosis: The seven pillars of RDoC. *BMC Medicine*, *11*(1), 126. https://doi.org/10.1186/1741-7015-11-126

Cutler, D. M. (2020). Early Returns from the Era of Precision Medicine. In *JAMA - Journal of the American Medical Association* (Vol. 323, Issue 2, pp. 109–110). American Medical Association. https://doi.org/10.1001/jama.2019.20659

Dar-Nimrod, I., Cheung, B. Y., Ruby, M. B., & Heine, S. J. (2014). Can merely learning about obesity genes affect eating behavior? *Appetite*, *81*, 269–276. https://doi.org/10.1016/j.appet.2014.06.109

Davidson, J. R. T. (2010). Major Depressive Disorder Treatment Guidelines in America and Europe. *The Journal of Clinical Psychiatry*, *71*(suppl E1). https://doi.org/10.4088/jcp.9058se1c.04gry

De Craen, A. J. M., Tijssen, J. G. P., De Gans, J., & Kleijnen, J. (2000). Placebo effect in the acute treatment of migraine: Subcutaneous placebos are better than oral placebos. *Journal of Neurology*, *247*(3), 183–188. https://doi.org/10.1007/s004150050560

de Maat, S. M., Dekker, J., Schoevers, R. A., & de Jonghe, F. (2006). Relative efficacy of psychotherapy and combined therapy in the treatment of depression: A meta-analysis. In *European Psychiatry* (Vol. 22, Issue 1, pp. 1–8). Eur Psychiatry. https://doi.org/10.1016/j.eurpsy.2006.10.008

Deloitte. (2015). *Made-to-order: The rise of mass personalisation. The Deloitte Consumer Review* . http://www.deloitte.com/view/consumerreview

Devilly, G. J., & Borkovec, T. D. (2000). Psychometric properties of the credibility/expectancy questionnaire. *Journal of Behavior Therapy and Experimental Psychiatry*, *31*(2), 73–86. https://doi.org/10.1016/S0005-7916(00)00012-4

Dunn, A. L., Trivedi, M. H., Kampert, J. B., Clark, C. G., & Chambliss, H. O. (2005). Exercise treatment for depression: Efficacy and dose response. *American Journal of Preventive Medicine*, *28*(1), 1–8. https://doi.org/10.1016/j.amepre.2004.09.003

Espay, A. J., Norris, M. M., Eliassen, J. C., Dwivedi, A., Smith, M. S., Banks, C., Allendorfer, J. B., Lang, A. E., Fleck, D. E., Linke, M. J., & Szaflarski, J. P. (2015). Placebo effect of medication cost in Parkinson disease: A randomized double-blind study. *Neurology*, *84*(8), 794–802. https://doi.org/10.1212/WNL.0000000000001282

Evers, A. W. M., Colloca, L., Blease, C., Annoni, M., Atlas, L. Y., Benedetti, F., Bingel, U., Büchel, C., Carvalho, C., Colagiuri, B., Crum, A. J., Enck, P., Gaab, J., Geers, A. L., Howick, J., Jensen, K. B., Kirsch, I., Meissner, K., Napadow, V., … Kelley, J. M. (2018). Implications of Placebo and Nocebo Effects for Clinical Practice: Expert Consensus. *Psychotherapy and Psychosomatics*, *87*(4), 204–210. https://doi.org/10.1159/000490354

Fässler, M., Gnädinger, M., Rosemann, T., & Biller-Andorno, N. (2011). Placebo interventions in practice: A questionnaire survey on the attitudes of patients and physicians. *British Journal of General Practice*, *61*(583), 101–107. https://doi.org/10.3399/bjgp11X556209

Fava, G. A., Guidi, J., Rafanelli, C., & Rickels, K. (2017). The Clinical Inadequacy of the Placebo Model and the Development of an Alternative Conceptual Framework. *Psychotherapy and Psychosomatics*, *86*(6), 332–340. https://doi.org/10.1159/000480038

Feczko, E., Miranda-Dominguez, O., Marr, M., Graham, A. M., Nigg, J. T., & Fair, D. A. (2019). The Heterogeneity Problem: Approaches to Identify Psychiatric Subtypes. In *Trends in Cognitive Sciences* (Vol. 23, Issue 7, pp. 584–601). Elsevier Ltd. https://doi.org/10.1016/j.tics.2019.03.009

Fernandes, B. S., Williams, L. M., Steiner, J., Leboyer, M., Carvalho, A. F., & Berk, M. (2017). The new field of "precision psychiatry." *BMC Medicine*, *15*(1), 80. https://doi.org/10.1186/s12916-017-0849-x

Finniss, D. G., Kaptchuk, T. J., Miller, F., & Benedetti, F. (2010). Biological, clinical, and ethical advances of placebo effects. In *The Lancet* (Vol. 375, Issue 9715, pp. 686–695). Elsevier. https://doi.org/10.1016/S0140-6736(09)61706-2

Forsberg, J. T., Martinussen, M., & Flaten, M. A. (2017). The Placebo Analgesic Effect in Healthy Individuals and Patients: A meta-analysis. *Psychosomatic Medicine*, *79*(4), 388–394. https://doi.org/10.1097/PSY.0000000000000432

Fountoulakis, K. N., & Rgen Möller, H.-J. (2012). Antidepressant drugs and the response in the placebo group: the real problem lies in our understanding of the issue. *Journal of Psychopharmacology*, *26*(5), 744–750. https://doi.org/10.1177/0269881111421969

Frances, A. (2013). The past, present and future of psychiatric diagnosis. In *World Psychiatry* (Vol. 12, Issue 2, pp. 111–112). World Psychiatric Association. https://doi.org/10.1002/wps.20027

Fried, E. I., & Nesse, R. M. (2015). Depression is not a consistent syndrome: An investigation of unique symptom patterns in the STAR∗D study. *Journal of Affective Disorders*, *172*, 96–102. https://doi.org/10.1016/j.jad.2014.10.010

Frisaldi, E., Shaibani, A., & Benedetti, F. (2020). Understanding the mechanisms of placebo and nocebo effects. *Swiss Medical Weekly*, *150*(35–36). https://doi.org/10.4414/smw.2020.20340

Gaynes, B. N., Warden, D., Trivedi, M. H., Wisniewski, S. R., Fava, M., & Rush, A. J. (2009). What did STAR*D teach us? Results from a large-scale, practical, clinical trial for patients with depression. In *Psychiatric Services* (Vol. 60, Issue 11, pp. 1439–1445). American Psychiatric Association. https://doi.org/10.1176/ps.2009.60.11.1439

Gelenberg, A. J., Marlene Freeman, C. P., Markowitz, J. C., Rosenbaum, J. F., Thase, M. E., Trivedi, M. H., Van Rhoads, R. S., Reus, V. I., Raymond DePaulo, C. J., Fawcett, J. A., Schneck, C. D., & Silbersweig, D. A. (2010). *Practice Guideline for the Treatment of Patients With Major Depressive Disorder. Third Edition.* http://www.psychiatryonline.com/pracGuide/pracGuideTopic_7.aspx.

Hardy, S. J., Krull, K. R., Wefel, J. S., & Janelsins, M. (2018). Cognitive Changes in Cancer Survivors. *American Society of Clinical Oncology Educational Book*, *38*, 795–806. https://doi.org/10.1200/edbk_201179

Harmer, C. J., Duman, R. S., & Cowen, P. J. (2017). How do antidepressants work? New perspectives for refining future treatment approaches. In *The Lancet Psychiatry* (Vol. 4, Issue 5, pp. 409–418). Elsevier Ltd. https://doi.org/10.1016/S2215-0366(17)30015-9

Heinemann, V., Douillard, J. Y., Ducreux, M., & Peeters, M. (2013). Targeted therapy in metastatic colorectal cancer - An example of personalised medicine in action. In *Cancer Treatment Reviews* (Vol. 39, Issue 6, pp. 592–601). W.B. Saunders. https://doi.org/10.1016/j.ctrv.2012.12.011

Hieronymus, F., Lisinski, A., Nilsson, S., & Eriksson, E. (2018). Efficacy of selective serotonin reuptake inhibitors in the absence of side effects: a mega-analysis of citalopram and paroxetine in adult depression. *Molecular Psychiatry*, *23*(8), 1731–1736. https://doi.org/10.1038/mp.2017.147

Horder, J., Matthews, P., & Waldmann, R. (2011). Placebo, Prozac and PLoS: Significant lessons for psychopharmacology. In *Journal of Psychopharmacology* (Vol. 25, Issue 10, pp. 1277–1288). J Psychopharmacol. https://doi.org/10.1177/0269881110372544

Howe, L. C., Goyer, J. P., & Crum, A. J. (2017). Harnessing the Placebo Effect: Exploring the Influence of Physician Characteristics on Placebo Response. *Health Psychology*. https://doi.org/10.1037/hea0000499

Howe, L. C., Leibowitz, K. A., & Crum, A. J. (2019). When your doctor “Gets it” and “Gets

you": The critical role of competence and warmth in the patient-provider interaction. *Frontiers in Psychiatry*, *10*(JULY). https://doi.org/10.3389/fpsyt.2019.00475

Hróbjartsson, A., & Gøtzsche, P. C. (2010). Placebo interventions for all clinical conditions. In *Cochrane Database of Systematic Reviews* (Vol. 2010, Issue 1). John Wiley and Sons Ltd. https://doi.org/10.1002/14651858.CD003974.pub3

Hróbjartsson, A., Kaptchuk, T. J., & Miller, F. G. (2011). Placebo effect studies are susceptible to response bias and to other types of biases. *Journal of Clinical Epidemiology*, *64*(11), 1223–1229. https://doi.org/10.1016/j.jclinepi.2011.01.008

Huibers, M. J. H., Cohen, Z. D., Lemmens, L. H. J. M., Arntz, A., Peeters, F. P. M. L., Cuijpers, P., & DeRubeis, R. J. (2015). Predicting optimal outcomes in cognitive therapy or interpersonal psychotherapy for depressed individuals using the personalized advantage index approach. *PLoS ONE*, *10*(11). https://doi.org/10.1371/journal.pone.0140771

Hull, S. C., Colloca, L., Avins, A., Gordon, N. P., Somkin, C. P., Kaptchuk, T. J., & Miller, F. G. (2013). Patients' attitudes about the use of placebo treatments:Telephone survey. *BMJ (Online)*, *347*(7915). https://doi.org/10.1136/bmj.f3757

Imel, Z. E., Malterer, M. B., McKay, K. M., & Wampold, B. E. (2008). A meta-analysis of psychotherapy and medication in unipolar depression and dysthymia. In *Journal of Affective Disorders* (Vol. 110, Issue 3, pp. 197–206). Elsevier. https://doi.org/10.1016/j.jad.2008.03.018

Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D. S., Quinn, K., Sanislow, C., & Wang, P. (2010). Research Domain Criteria (RDoC): Toward a new classification framework for research on mental disorders. In *American Journal of Psychiatry* (Vol. 167, Issue 7, pp. 748–751). American Psychiatric Association . https://doi.org/10.1176/appi.ajp.2010.09091379

Insel, T. R. (2014). The NIMH Research Domain Criteria (RDOC) Project: Precision Medicine for Psychiatry. In *American Journal of Psychiatry* (Vol. 171, Issue 4, pp. 395–397). American Psychiatric Association. https://doi.org/10.1176/appi.ajp.2014.14020138

Insel, T. R., & Cuthbert, B. N. (2015). Brain disorders? Precisely: Precision medicine comes to psychiatry. *Science*, *348*(6234), 499–500. https://doi.org/10.1126/science.aab2358

Ioannidis, J. P. A. (2008). Why most discovered true associations are inflated. *Epidemiology*, *19*(5), 640–648. https://doi.org/10.1097/EDE.0b013e31818131e7

Issa, A. M., Tufail, W., Hutchinson, J., Tenorio, J., & Poonam Baliga, M. (2009). Assessing Patient Readiness for the Clinical Adoption of Personalized Medicine. *Public Health Genomics*, *12*, 163–169. https://doi.org/10.1159/000189629

Jepma, M., Jones, M., & Wager, T. D. (2014). The dynamics of pain: Evidence for simultaneous site-specific habituation and site-nonspecific sensitization in thermal pain. *Journal of Pain*, *15*(7), 734–746. https://doi.org/10.1016/j.jpain.2014.02.010

John, O. P., Donahue, E. M., & Kentle, R. L. (1991). *Big Five Inventory*. https://psycnet.apa.org/doiLanding?doi=10.1037%2Ft07550-000

John, O., & Srivastava, S. (1999). *The Big-Five trait taxonomy: History, measurement, and theoretical perspectives*. http://t.personality-project.org/revelle/syllabi/classreadings/john.pdf

John Rush, A., Trivedi, M. H., Wisniewski, S. R., Nierenberg, A. A., Stewart, J. W., Warden, D., George Niederehe, M., Thase, M. E., Lavori, P. W., Lebowitz, B. D., McGrath, P. J., Rosenbaum, J. F., Sackeim, H. A., Kupfer, D. J., Luther, J., & Maurizio Fava, M. (2006). Acute and Longer-Term Outcomes in Depressed Outpatients Requiring One or Several Treatment Steps: A STAR*D Report. In *Am J Psychiatry* (Vol. 163, Issue 11). www.star-d.org

Juengst, E., McGowan, M. L., Fishman, J. R., & Settersten, R. A. (2016). From "Personalized" to "Precision" Medicine: The Ethical and Social Implications of Rhetorical Reform in Genomic Medicine. *Hastings Center Report*, *46*(5), 21–33. https://doi.org/10.1002/hast.614

Kamenov, K., Twomey, C., Cabello, M., Prina, A. M., & Ayuso-Mateos, J. L. (2017). *The efficacy of psychotherapy, pharmacotherapy and their combination on functioning and quality of life in depression: a meta-analysis*. *47*, 414–425. https://doi.org/10.1017/S0033291716002774

Kaptchuk, T. J. (2002). The placebo effect in alternative medicine: Can the performance of a healing ritual have clinical significance? *Annals of Internal Medicine*, *136*(11), 817–825. https://doi.org/10.7326/0003-4819-136-11-200206040-00011

Kaptchuk, T. J., Goldman, P., Stone, D. A., & Stason, W. B. (2000). Do medical devices have enhanced placebo effects? *Journal of Clinical Epidemiology*, *53*(8), 786–792. https://doi.org/10.1016/S0895-4356(00)00206-7

Kaptchuk, T. J., Hemond, C. C., & Miller, F. G. (2020). Placebos in chronic pain: Evidence, theory, ethics, and use in clinical practice. In *The BMJ* (Vol. 370, p. 1668). BMJ Publishing Group. https://doi.org/10.1136/bmj.m1668

Kaptchuk, T. J., Kelley, J. M., Conboy, L. A., Davis, R. B., Kerr, C. E., Jacobson, E. E., Kirsch, I., Schyner, R. N., Bong, H. N., Nguyen, L. T., Park, M., Rivers, A. L., McManus, C., Kokkotou, E., Drossman, D. A., Goldman, P., & Lembo, A. J. (2008). Components of placebo effect: Randomised controlled trial in patients with irritable bowel syndrome. *BMJ*, *336*(7651), 999–1003. https://doi.org/10.1136/bmj.39524.439618.25

Kaptchuk, T. J., Stason, W. B., Davis, R. B., Legedza, A. T. R., Schnyer, R. N., Kerr, C. E., Stone, D. A., Nam, B. H., Kirsch, I., & Goldman, R. H. (2006). Sham device v inert pill: randomised controlled trial of two placebo treatments. *BMJ*, *332*(7538), 391–397. https://doi.org/10.1136/bmj.38726.603310.55

Kato, S., Kim, K., Lim, H., … A. B.-N., & 2020, U. (2020). Real-world data from a molecular tumor board demonstrates improved outcomes with a precision N-of-One strategy. *Nature.Com*, *11*. https://www.nature.com/articles/s41467-020-18613-3

Kemp, J. J., Lickel, J. J., & Deacon, B. J. (2014). Effects of a chemical imbalance causal explanation on individuals' perceptions of their depressive symptoms. *Behaviour Research and Therapy*, *56*(1), 47–52. https://doi.org/10.1016/j.brat.2014.02.009

Kessler, R. C. (2003). Epidemiology of women and depression. *Journal of Affective Disorders*, *74*(1), 5–13. https://doi.org/10.1016/S0165-0327(02)00426-3

Kirsch, I. (2005). Placebo psychotherapy: Synonym or oxymoron? *Journal of Clinical Psychology*, *61*(7), 791–803. https://doi.org/10.1002/jclp.20126

Kirsch, I., Deacon, B. J., Huedo-Medina, T. B., Scoboria, A., Moore, T. J., & Johnson, B. T. (2008). Initial Severity and Antidepressant Benefits: A Meta-Analysis of Data Submitted to the Food and Drug Administration. *PLoS Medicine*, *5*(2), e45. https://doi.org/10.1371/journal.pmed.0050045

Kirsch, I., Moore, T. J., Scoboria, A., & Nicholls, S. S. (2002). The Emperor's New Drugs: An Analysis of Antidepressant Medication Data Submitted to the U.S. Food and Drug Administration. In *Prevention & Treatment* (Vol. 5, Issue 23).

Kirsch, I., & Sapirstein, G. (1998). Listening to Prozac but Hearing Placebo: A Meta-Analysis of Antidepressant Medication. *Prevention & Treatment*, *1*. http://journals.apa.org/pt/prevention/volume1/pre0010002a.html

Kohut, K., Limb, S., & Crawford, G. (2019). The Changing Role of the Genetic Counsellor in the Genomics Era. *Current Genetic Medicine Reports*, *7*(2), 75–84. https://doi.org/10.1007/s40142-019-00163-w

Kornhaber, R., Walsh, K., Duff, J., & Walker, K. (2016). Enhancing adult therapeutic interpersonal relationships in the acute health care setting: An integrative review. In *Journal of Multidisciplinary Healthcare* (Vol. 9, pp. 537–546). Dove Medical Press Ltd. https://doi.org/10.2147/JMDH.S116957

Kovacs, G. (2016). Molecular Pathological Classification of Neurodegenerative Diseases: Turning towards Precision Medicine. *International Journal of Molecular Sciences*, *17*(2), 189. https://doi.org/10.3390/ijms17020189

Krystal, A. D., Pizzagalli, D. A., Smoski, M., Mathew, S. J., Nurnberger, J., Lisanby, S. H., Iosifescu, D., Murrough, J. W., Yang, H., Weiner, R. D., Calabrese, J. R., Sanacora, G., Hermes, G., Keefe, R. S. E., Song, A., Goodman, W., Szabo, S. T., Whitton, A. E., Gao, K., & Potter, W. Z. (2020). A randomized proof-of-mechanism trial applying the 'fast-fail' approach to evaluating κ-opioid antagonism as a treatment for anhedonia. *Nature Medicine*, *26*(5), 760–768. https://doi.org/10.1038/s41591-020-0806-7

Kvam, S., Kleppe, C. L., Nordhus, I. H., & Hovland, A. (2016). Exercise as a treatment for depression: A meta-analysis. In *Journal of Affective Disorders* (Vol. 202, pp. 67–86). Elsevier B.V. https://doi.org/10.1016/j.jad.2016.03.063

Laska, K. M., Gurman, A. S., & Wampold, B. E. (2014). Expanding the lens of evidence-based practice in psychotherapy: A common factors perspective. *Psychotherapy*, *51*(4), 467–481. https://doi.org/10.1037/a0034332

Lebowitz, M. S. (2019). The Implications of Genetic and Other Biological Explanations for Thinking about Mental Disorders. *Hastings Center Report*, *49*(S1), S82–S87. https://doi.org/10.1002/hast.1020

Lebowitz, M. S., Ahn, W. K., & Nolen-Hoeksema, S. (2013). Fixable or fate? Perceptions of the biology of depression. *Journal of Consulting and Clinical Psychology*, *81*(3), 518–527. https://doi.org/10.1037/a0031730

Lebowitz, M. S., & Ahn, W. kyoung. (2015). Emphasizing Malleability in the biology of depression: Durable effects on perceived agency and prognostic pessimism. *Behaviour Research and Therapy*, *71*, 125–130. https://doi.org/10.1016/j.brat.2015.06.005

Lee, Y., Ragguett, R. M., Mansur, R. B., Boutilier, J. J., Rosenblat, J. D., Trevizol, A., Brietzke, E., Lin, K., Pan, Z., Subramaniapillai, M., Chan, T. C. Y., Fus, D., Park, C., Musial, N., Zuckerman, H., Chen, V. C. H., Ho, R., Rong, C., & McIntyre, R. S. (2018). Applications of machine learning algorithms to predict therapeutic outcomes in depression: A meta-analysis and systematic review. In *Journal of Affective Disorders* (Vol. 241, pp. 519–532). Elsevier B.V. https://doi.org/10.1016/j.jad.2018.08.073

Lim, G. Y., Tam, W. W., Lu, Y., Ho, C. S., Zhang, M. W., & Ho, R. C. (2018). Prevalence of Depression in the Community from 30 Countries between 1994 and 2014 /692/699/476/1414 /692/499 article. *Scientific Reports*, *8*(1), 1–10. https://doi.org/10.1038/s41598-018-21243-x

Lindheimer, J. B., O'Connor, P. J., & Dishman, R. K. (2015). Quantifying the Placebo Effect in Psychological Outcomes of Exercise Training: A Meta-Analysis of Randomized Trials. In *Sports Medicine* (Vol. 45, Issue 5, pp. 693–711). Springer International Publishing. https://doi.org/10.1007/s40279-015-0303-1

Matuszak, J., & Piasecki, M. (2012). Inter-Rater Reliability in Psychiatric Diagnosis. *Psychiatric Times*, *29*(10). https://www.psychiatrictimes.com/view/inter-rater-reliability-psychiatric-diagnosis

McNeil, D. W., & Rainwater, A. J. (1998). Development of the fear of pain questionnaire - III. *Journal of Behavioral Medicine*, *21*(4), 389–410. https://doi.org/10.1023/A:1018782831217

Mehling, W. E., Price, C., Daubenmier, J. J., Acree, M., Bartmess, E., & Stewart, A. (2012). The Multidimensional Assessment of Interoceptive Awareness (MAIA). *PLoS ONE*, *7*(11), e48230. https://doi.org/10.1371/journal.pone.0048230

Meiser, B., Irle, J., Lobb, E., & Barlow-Stewart, K. (2008). Assessment of the content and process of genetic counseling: A critical review of empirical studies. In *Journal of Genetic Counseling* (Vol. 17, Issue 5, pp. 434–451). John Wiley & Sons, Ltd. https://doi.org/10.1007/s10897-008-9173-0

Meissner, K., Fässler, M., Rücker, G., Kleijnen, J., Hróbjartsson, A., Schneider, A., Antes, G., & Linde, K. (2013). Differential effectiveness of placebo treatments: A systematic review of migraine prophylaxis. *JAMA Internal Medicine*, *173*(21), 1941–1951. https://doi.org/10.1001/jamainternmed.2013.10391

Miller, F. A., Hayeems, R. Z., Bytautas, J. P., Bedard, P. L., Ernst, S., Hirte, H., Hotte, S., Oza, A., Razak, A., Welch, S., Winquist, E., Dancey, J., & Siu, L. L. (2014). Testing personalized medicine: Patient and physician expectations of next-generation genomic sequencing in late-stage cancer care. *European Journal of Human Genetics*, *22*(3), 391–

395. https://doi.org/10.1038/ejhg.2013.158

Miller, F. G., Wendler, D., & Swartzman, L. C. (2005). Deception in research on the placebo effect. In *PLoS Medicine* (Vol. 2, Issue 9, pp. 0853–0859). Public Library of Science. https://doi.org/10.1371/journal.pmed.0020262

Montgomery, G. H., & Kirsch, I. (1997). Classical conditioning and the placebo effect. *PAIN*, *72*(1–2), 107–113. https://doi.org/10.1016/S0304-3959(97)00016-X

Mota-Pereira, J., Silverio, J., Carvalho, S., Ribeiro, J. C., Fonte, D., & Ramos, J. (2011). Moderate exercise improves depression parameters in treatment-resistant patients with major depressive disorder. *Journal of Psychiatric Research*, *45*(8), 1005–1011. https://doi.org/10.1016/j.jpsychires.2011.02.005

Murray, D., & Stoessl, A. J. (2013). Mechanisms and therapeutic implications of the placebo effect in neurological and psychiatric conditions. In *Pharmacology and Therapeutics* (Vol. 140, Issue 3, pp. 306–318). Elsevier Inc. https://doi.org/10.1016/j.pharmthera.2013.07.009

National Cancer Institute. (2017, October). *Tumor DNA Sequencing in Cancer Treatment*. https://www.cancer.gov/about-cancer/treatment/types/precision-medicine/tumor-dna-sequencing

National Cancer Institute. (2021). *Targeted Cancer Therapies Fact Sheet*. https://www.cancer.gov/about-cancer/treatment/types/targeted-therapies/targeted-therapies-fact-sheet

Nichols, A. L., & Edlund, J. E. (2015). Practicing What We Preach (and Sometimes Study): Methodological Issues in Experimental Laboratory Research. *Review of General Psychology*, *19*(2), 191–202. https://doi.org/10.1037/gpr0000027

Nunes, A., Ardau, R., Berghöfer, A., Bocchetta, A., Chillotti, C., Deiana, V., Garnham, J., Grof, E., Hajek, T., Manchia, M., Müller-Oerlinghausen, B., Pinna, M., Pisanu, C., O'Donovan, C., Severino, G., Slaney, C., Suwalska, A., Zvolsky, P., Cervantes, P., … Alda, M. (2020). Prediction of lithium response using clinical data. *Acta Psychiatrica Scandinavica*, *141*(2), 131–141. https://doi.org/10.1111/acps.13122

Nusslock, R., & Alloy, L. B. (2017). Reward processing and mood-related symptoms: An RDoC and translational neuroscience perspective. In *Journal of Affective Disorders* (Vol. 216, pp. 3–16). Elsevier B.V. https://doi.org/10.1016/j.jad.2017.02.001

Ogihara, Y., Fujita, H., Tominaga, H., Ishigaki, S., Kashimoto, T., Takahashi, A., Toyohara, K., & Uchida, Y. (2015). Are common names becoming less common? The rise in uniqueness and individualism in Japan. *Frontiers in Psychology*, *6*(OCT), 1490. https://doi.org/10.3389/fpsyg.2015.01490

Olson, J. A., Lifshitz, M., Raz, A., & Veissière, S. P. L. (2021). Super Placebos: A Feasibility Study Combining Contextual Factors to Promote Placebo Effects. *Frontiers in Psychiatry*, *12*, 644825. https://doi.org/10.3389/fpsyt.2021.644825

Olson, J. A., & Raz, A. (2021). Applying insights from magic to improve deception in research: The Swiss cheese model. *Journal of Experimental Social Psychology*, *92*, 104053.

https://doi.org/10.1016/j.jesp.2020.104053

Paterson, C., & Dieppe, P. (2005). Characteristic and incidental (placebo) effects in complex interventions such as acupuncture. *British Medical Journal*, *330*, 1202–1205. https://doi.org/10.1136/bmj.330.7501.1202

Patten, S. B., Li Wang, J., Williams, J. V., Currie, S., Beck, C. A., Maxwell, C. J., & el-Guebaly, N. (2006). Descriptive Epidemiology of Major Depression in Canada. In *Can J Psychiatry* (Vol. 51, Issue 2).

Paucek, R. D., Baltimore, D., & Li, G. (2019). The Cellular Immunotherapy Revolution: Arming the Immune System for Precision Therapy. In *Trends in Immunology* (Vol. 40, Issue 4, pp. 292–309). Elsevier Ltd. https://doi.org/10.1016/j.it.2019.02.002

Paul, J., Metcalfe, S., Stirling, L., Wilson, B., & Hodgson, J. (2015). Analyzing communication in genetic consultations-A systematic review. In *Patient Education and Counseling* (Vol. 98, Issue 1, pp. 15–33). Elsevier Ireland Ltd. https://doi.org/10.1016/j.pec.2014.09.017

Peerdeman, K. J., Van Laarhoven, A. I. M., Keij, S. M., Vase, L., Rovers, M. M., Peters, M. L., & Evers, A. W. M. (2016). Relieving patients' pain with expectation interventions: A meta-analysis. In *Pain* (Vol. 157, Issue 6, pp. 1179–1191). Lippincott Williams and Wilkins. https://doi.org/10.1097/j.pain.0000000000000540

Peirce, J. W. (2009). Generating stimuli for neuroscience using PsychoPy. *Frontiers in Neuroinformatics*, *2*(JAN). https://doi.org/10.3389/neuro.11.010.2008

Pescosolido, B. A., Martin, J. K., Long, J. S., Medina, T. R., Phelan, J. C., & Link, B. G. (2010). "A disease like any other"? a decade of change in public reactions to schizophrenia, depression, and alcohol dependence. *American Journal of Psychiatry*, *167*(11), 1321–1330. https://doi.org/10.1176/appi.ajp.2010.09121743

Pollo, A., Amanzio, M., Arslanian, A., Casadio, C., Maggi, G., & Benedetti, F. (2001). Response expectancies in placebo analgesia and their clinical relevance. *Pain*, *93*(1), 77–84. https://doi.org/10.1016/S0304-3959(01)00296-2

Price, D. D., Finniss, D. G., & Benedetti, F. (2007). *A Comprehensive Review of the Placebo Effect: Recent Advances and Current Thought*. https://doi.org/10.1146/annurev.psych.59.113006.095941

Quattrone, A., Barbagallo, G., Cerasa, A., & Stoessl, A. J. (2018). *Neurobiology of Placebo Effect in Parkinson's Disease: What We Have Learned and Where We Are Going*. https://doi.org/10.1002/mds.27438

Rajpurkar, P., Yang, J., Dass, N., Vale, V., Keller, A. S., Irvin, J., Taylor, Z., Basu, S., Ng, A., & Williams, L. M. (2020). Evaluation of a Machine Learning Model Based on Pretreatment Symptoms and Electroencephalographic Features to Predict Outcomes of Antidepressant Treatment in Adults With Depression: A Prespecified Secondary Analysis of a Randomized Clinical Trial. *JAMA Network Open*, *3*(6), e206653. https://doi.org/10.1001/jamanetworkopen.2020.6653

Rieder, M. J., Reiner, A. P., Gage, B. F., Nickerson, D. A., Eby, C. S., McLeod, H. L., Blough,

D. K., Thummel, K. E., Veenstra, D. L., & Rettie, A. E. (2005). Effect of VKORC1 Haplotypes on Transcriptional Regulation and Warfarin Dose . *New England Journal of Medicine*, *352*(22), 2285–2293. https://doi.org/10.1056/nejmoa044503

Rief, W., Nestoriuc, Y., Weiss, S., Welzel, E., Barsky, A. J., & Hofmann, S. G. (2009). Meta-analysis of the placebo response in antidepressant trials. In *Journal of Affective Disorders* (Vol. 118, Issues 1–3, pp. 1–8). Elsevier. https://doi.org/10.1016/j.jad.2009.01.029

Rimer, J., Dwan, K., Lawlor, D. A., Greig, C. A., McMurdo, M., Morley, W., & Mead, G. E. (2012). Exercise for depression. In *Cochrane Database of Systematic Reviews* (Issue 7). John Wiley & Sons, Ltd. https://doi.org/10.1002/14651858.cd004366.pub5

Rosenberg, J. (2019). *FDA Approves Gene Therapy With $2.1M Price Tag for Spinal Muscular Atrophy in Pediatric Patients*. AJMC. https://www.ajmc.com/view/fda-approves-gene-therapy-with-21m-price-tag-for-spinal-muscular-atrophy-in-pediatric-patients

Rosenzweig, S. (1936). Some implicit common factors in diverse methods of psychotherapy. *American Journal of Orthopsychiatry*, *6*(3), 412–415. https://doi.org/10.1111/j.1939-0025.1936.tb05248.x

Sandler, A. D., Glesne, C. E., & Bodfish, J. W. (2010). Conditioned placebo dose reduction: A new treatment in attention-deficit hyperactivity disorder? *Journal of Developmental and Behavioral Pediatrics*, *31*(5), 369–375. https://doi.org/10.1097/DBP.0b013e3181e121ed

Santos, H. C., Varnum, M. E. W., & Grossmann, I. (2017). Global Increases in Individualism. *Psychological Science*, *28*(9), 1228–1239. https://doi.org/10.1177/0956797617700622

Schuch, F. B., Vasconcelos-Moreno, M. P., Borowsky, C., & Fleck, M. P. (2011). Exercise and severe depression: Preliminary results of an add-on study. *Journal of Affective Disorders*, *133*(3), 615–618. https://doi.org/10.1016/j.jad.2011.04.030

Schuch, F. B., Vasconcelos-Moreno, M. P., Borowsky, C., Zimmermann, A. B., Rocha, N. S., & Fleck, M. P. (2015). Exercise and severe major depression: Effect on symptom severity and quality of life at discharge in an inpatient cohort. *Journal of Psychiatric Research*, *61*, 25–32. https://doi.org/10.1016/j.jpsychires.2014.11.005

Schuch, Felipe B., Vancampfort, D., Richards, J., Rosenbaum, S., Ward, P. B., & Stubbs, B. (2016). Exercise as a treatment for depression: A meta-analysis adjusting for publication bias. *Journal of Psychiatric Research*, *77*, 42–51. https://doi.org/10.1016/j.jpsychires.2016.02.023

Shah, K. R., & Goold, S. D. (2009). The primacy of autonomy, honesty, and disclosure-council on ethical and judicial affairs' placebo opinions. *American Journal of Bioethics*, *9*(12), 15–17. https://doi.org/10.1080/15265160903316339

Sliwinski, J., & Elkins, G. R. (2013). Enhancing Placebo Effects: Insights From Social Psychology. *American Journal of Clinical Hypnosis* , *55*, 236–248. https://doi.org/10.1080/00029157.2012.740434

Snyder, C. R., & Fromkin, H. L. (1977). Abnormality as a positive characteristic: The development and validation of a scale measuring need for uniqueness. *Journal of Abnormal*

Psychology, *86*(5), 518–527. https://doi.org/10.1037/0021-843X.86.5.518

Spielmans, G. I., Berman, M. I., & Usitalo, A. N. (2011). Psychotherapy Versus Second-Generation Antidepressants in the Treatment of Depression: A Meta-Analysis. *J Nerv Ment Dis*, *199*, 142–149. https://doi.org/10.1097/NMD.0b013e31820caefb

Stanton, R., & Reaburn, P. (2014). Exercise and the treatment of depression: A review of the exercise program variables. In *Journal of Science and Medicine in Sport* (Vol. 17, Issue 2, pp. 177–182). Elsevier. https://doi.org/10.1016/j.jsams.2013.03.010

Strafella, C., Caputo, V., Galota, M. R., Zampatti, S., Marella, G., Mauriello, S., Cascella, R., & Giardina, E. (2018). Application of Precision Medicine in Neurodegenerative Diseases. *Frontiers in Neurology*, *9*(AUG), 701. https://doi.org/10.3389/fneur.2018.00701

Subramanian, M., Wojtusciszyn, A., Favre, L., Boughorbel, S., Shan, J., Letaief, K. B., Pitteloud, N., & Chouchane, L. (2020). Precision medicine in the era of artificial intelligence: implications in chronic disease management. In *Journal of Translational Medicine* (Vol. 18, Issue 1). BioMed Central Ltd. https://doi.org/10.1186/s12967-020-02658-5

Sullivan, M. J. L., Bishop, S. R., & Pivik, J. (1995). The Pain Catastrophizing Scale: Development and Validation. *Psychological Assessment*, *7*(4), 524–532. https://doi.org/10.1037/1040-3590.7.4.524

Swain, S. M., Baselga, J., Kim, S.-B., Ro, J., Semiglazov, V., Campone, M., Ciruelos, E., Ferrero, J.-M., Schneeweiss, A., Heeson, S., Clark, E., Ross, G., Benyunes, M. C., & Cortés, J. (2015). Pertuzumab, Trastuzumab, and Docetaxel in HER2-Positive Metastatic Breast Cancer. *New England Journal of Medicine*, *372*(8), 724–734. https://doi.org/10.1056/nejmoa1413513

Tabry, V., Vogel, T. A., Lussier, M., Brouillard, P., Buhle, J., Rainville, P., Bherer, L., & Roy, M. (2020). Inter-individual predictors of pain inhibition during performance of a competing cognitive task. *Scientific Reports*, *10*(1). https://doi.org/10.1038/s41598-020-78653-z

Teychenne, M., Ball, K., & Salmon, J. (2010). Sedentary Behavior and Depression Among Adults: A Review. *Int.J.Behav.Med.*, *17*, 246–254. https://doi.org/10.1007/s12529-010-9075-z

Thompson, E. R. (2007). *DEVELOPMENT AND VALIDATION OF AN INTERNATIONALLY RELIABLE SHORT-FORM OF THE POSITIVE AND NEGATIVE AFFECT SCHEDULE (PANAS)*. https://doi.org/10.1177/0022022106297301

Trivedi, M. H. (2016). Right patient, right treatment, right time: biosignatures and precision medicine in depression. In *World Psychiatry* (Vol. 15, Issue 3, pp. 237–238). Blackwell Publishing Ltd. https://doi.org/10.1002/wps.20371

Turnwald, B. P., Goyer, J. P., Boles, D. Z., Silder, A., Delp, S. L., & Crum, A. J. (2019). Learning one's genetic risk changes physiology independent of actual genetic risk. In *Nature Human Behaviour* (Vol. 3, Issue 1, pp. 48–56). Nature Publishing Group. https://doi.org/10.1038/s41562-018-0483-4

van Bronswijk, S. C., DeRubeis, R. J., Lemmens, L. H. J. M., Peeters, F. P. M. L., Keefe, J. R.,

Cohen, Z. D., & Huibers, M. J. H. (2019). Precision medicine for long-term depression outcomes using the Personalized Advantage Index approach: cognitive therapy or interpersonal psychotherapy? *Psychological Medicine*, *51*(2), 1–11. https://doi.org/10.1017/s0033291719003192

Vase, L., Robinson, M. E., Verne, G. N., & Price, D. D. (2005). Increased placebo analgesia over time in irritable bowel syndrome (IBS) patients is associated with desire and expectation but not endogenous opioid mechanisms. *Pain*, *115*(3), 338–347. https://doi.org/10.1016/j.pain.2005.03.014

von Wernsdorff, M., Loef, M., Tuschen-Caffier, B., & Schmidt, S. (2021). Effects of open-label placebos in clinical trials: a systematic review and meta-analysis. *Scientific Reports*, *11*(1), 3855. https://doi.org/10.1038/s41598-021-83148-6

Waber, R. L., Shiv, B., Carmon, Z., & Ariely, D. (2008). Commercial features of placebo and therapeutic efficacy. In *JAMA - Journal of the American Medical Association* (Vol. 299, Issue 9, pp. 1016–1017). American Medical Association. https://doi.org/10.1001/jama.299.9.1016

Wager, T. D. (2005). Expectations and anxiety as mediators of placebo effects in pain. *Pain*, *115*(3), 225–226. https://doi.org/10.1016/j.pain.2005.03.018

Wager, T. D., Atlas, L. Y., Leotti, L. A., & Rilling, J. K. (2011). *Predicting Individual Differences in Placebo Analgesia: Contributions of Brain Activity during Anticipation and Pain Experience*. https://doi.org/10.1523/JNEUROSCI.3420-10.2011

Wager, T. D., Rilling, J. K., Smith, E. E., Sokolik, A., Casey, K. L., Davidson, R. J., Kosslyn, S. M., Rose, R. M., & Cohen, J. D. (2004). Placebo-Induced Changes in fMRI in the Anticipation and Experience of Pain. *Science*, *303*(5661), 1162–1167. https://doi.org/10.1126/science.1093065

Wampold, B. E. (2015). How important are the common factors in psychotherapy? An update. *World Psychiatry*, *14*(3), 270–277. https://doi.org/10.1002/wps.20238

Wampold, B. E., Minami, T., Tierney, S. C., Baskin, T. W., & Bhati, K. S. (2005). The placebo is powerful: Estimating placebo effects in medicine and psychotherapy from randomized clinical trials. *Journal of Clinical Psychology*, *61*(7), 835–854. https://doi.org/10.1002/jclp.20129

Weissman, M. M., & Olfson, M. (1995). Depression in Women: Implications for Health Care Research. *Science*. http://science.sciencemag.org/

World Health Organization. (2020). *Depression*. https://www.who.int/news-room/fact-sheets/detail/depression

Zhai, L., Zhang, Y., & Zhang, D. (2015). Sedentary behaviour and the risk of depression: a meta-analysis. *Br J Sports Med*, *49*, 705–709. https://doi.org/10.1136/bjsports-2014-093613

Zigmond, A. S., & Snaith, R. P. (1983). The Hospital Anxiety and Depression Scale. *Acta Psychiatrica Scandinavica*, *67*(6), 361–370. https://doi.org/10.1111/j.1600-0447.1983.tb09716.x

Appendices

Appendix A: Suggestions of tailoring (placebo machine)

Experimental. Alright, so you have the gene A, B, C…great, optimal level of C2 fibers.

[Go through the output and mark some things, then pretend you forgot the highlighter and step out leaving the output for them to look through.]

Alright, so let's go through this output here. [Explain the genes].

Now let's calibrate this Alpha-TENS to your profile.

[Next is said while you calibrate the machine from the personalized output]. So you know how when you hit your knee or your toe or something, you grab it and rub it a bit so it makes it hurt less? Yeah, by rubbing the hurt spot you activate the C2 fibers in your skin that dampen your pain response. So this machine works the same way, it activates your C2 fibers by sending a high frequency current and dampens your pain response. So the better it matches your profile, the better it dampens the response. So you feel less pain in the process. It's hard to calibrate the C2 fiber response though, but with this new genetic pain tolerance tests it makes it quicker to tailor the machine to you. Alright, it's all set. Do you have any other questions?

[Attach the electrodes to the participant, turn the TENS on to intensity 4, let them get used to it.] Does it feel okay? So this is the maximal intensity that the machine should be used at, but we will be using this intensity here [decrease the intensity to zero]. Does this feel alright? Okay. Mira will be with you in a minute. Let's just try the machine first, so that you know what it feels like during the test.

Control. [Glance at the clipboard for a bit, then put it on the table and sit in front of the participant.] Alright, it seems like everything is good and that you are eligible for the study.

So let's talk about the analgesic that we will be using today. It's called Alpha-TENS, have you heard of it before? No, ok, it's this machine that's been around for a while and is used mainly in hospitals to treat pain in patients. So you know how when you hit your knee or your toe or something, you grab it and rub it a bit so it makes it hurt less? Yeah, by rubbing the hurt spot you activate the C2 fibers in your skin that dampen your pain response. So this machine works the same way, it activates your C2 fibers by sending a high frequency current and dampens your pain response. So when the machine is active, you feel less pain. Do you have any questions about it before we start the study? No, ok.

Appendix B: False feedback

```
Subject:     Number:       8542
             Gender:       1
             Ethnicity:    3
             Source:       subjectpool
             Skin conduct: 0.5
             Skin imp:     4.3
             Calibration:  genespecifics[7item]
             Genes:        standardSel
```

RESULTS

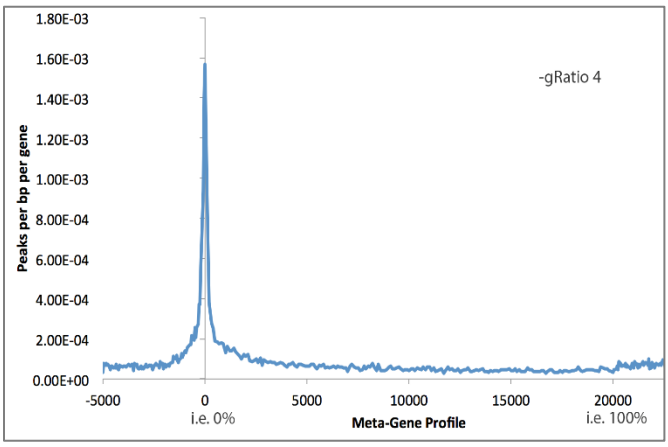
GENES	PHENOTYPES	GENOTYPES	TESTED ALLELES
KYP1A2	Inducible	*1F/*1F	*1C, *1F, *1K
KYP2B6	Poor conductor	*6/*6	*4, *6, *18
KYP2C19	Normal conductor	*1/*17	*2, *3, *4, *5, *6, *7, *8, *17
KYP2C9	Normal latency	*1/*1	*2, *3, *4, *5, *6, *8, *11, *12
KYP2D6	Normal latency	*1/*10	*2, *3, *4, *5, *6, *7, *8, *9, *10
KYP3A4	High latency	*17/*17	*2, *17, *22
OPRM1	-	AA	rs1799971

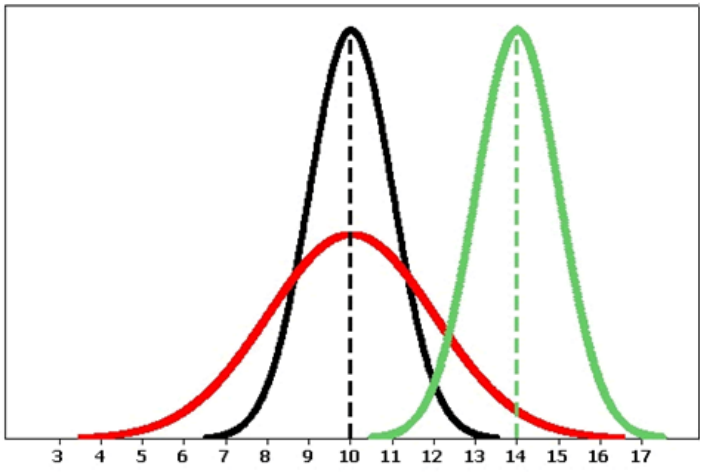
KYP1A2: Cytochrome P450 1A2; KYP2B6: Cytochrome P450 2B6; KYP2C19: Cytochrome P450 2C19; KYP2C9: Cytochrome P450 2C9; KYP2D6: Cytochrome P450 2D6; KYP3A4: Cytochrome P450 3A4; OPRM1: Opioid Receptor mu 1

Treatment frequency (Hz)	Treatment current (RMS) (mA)	Actual frequency (Hz)		Actual voltage (RMS) (V)		Actual current (RMS) (mA)		n
		Mean	SD	Mean	SD	Mean	SD	
200	100	207.8	6.11	167.5	11.64	101.0	2.45	6
	150	202.7	1.86	213.7	30.00	151.7	2.58	6
	200	204.4	2.93	257.1	36.59	199.1	2.42	8
400	100	401.9	1.81	167.5	17.74	99.0	2.33	8
	150	403.3	2.06	206.0	28.90	150.3	2.69	7
	200	403.6	4.00	279.1	27.69	198.4	4.57	8
600	100	604.9	2.80	144.4	13.10	99.0	1.63	7
	150	605.0	3.96	230.3	43.03	148.0	2.04	7
	200	602.1	1.89	285.3	37.50	198.8	6.41	8
800	100	802.5	1.52	157.8	23.65	97.0	2.10	6
	150	804.0	3.16	209.0	52.37	148.0	1.92	7
	200	805.6	2.64	276.9	10.48	199.6	5.88	7
1000	100	1004.6	3.10	142.1	14.84	96.6	1.27	7
	150	1003.7	3.93	226.8	35.12	145.8	3.06	6
	200	1004.6	3.57	272.6	31.24	198.8	4.33	8
1200	100	1204.5	4.28	144.1	19.68	96.5	3.54	10
	150	1210.6	8.70	213.6	18.88	143.0	8.10	7
	200	1200.2	6.52	266.0	24.23	195.2	6.04	8
1400	100	1403.8	2.05	134.1	24.14	96.0	1.87	9
	150	1401.5	1.93	214.3	36.10	143.6	5.73	8
	200	1402.7	2.23	274.9	48.28	193.6	5.68	8

Alpha-TENS-3000

```
Train rate (TPS):   8.5
Frequency:          100 Hz
Voltage:            4.9
S1:                 7
S2:                 5
Stimulation:        N
Pulse width:        0.9 ms
Speed rate:         x10
Fr dur:             x1
Pulses:             twin
Intensity:          4.5
```





Levels of evidence

1 - Recommendation based on pharmacogenetic information on the drug label approved by Health Canada and/or the US Food and Drug Administration (FDA). A level 1 will also be attributed if the recommendation originates from a clinical guideline published by the Clinical Pharmacogenetics Implementation Consortium (CPIC) or the Dutch Pharmacogenomics Working Group (DPWG).

2 - Recommendation based on the results of multiple studies showing a statistically significant effect of a genetic variant on drug response.

3 - Recommendation based on the results of a single study showing a statistically significant effect of a genetic variant on drug response and/or drug pharmacokinetics.

4 - Recommendation based only on knowledge of the principal metabolizing enzyme without in vivo or in vitro data demonstrating the impact that genetic variability has on drug response or pharmacokinetics.

Appendix C: Measures Study 1

Need for Uniqueness Questionnaire

The following statements concern your perceptions about yourself in a variety of situations. Your task is to indicate the strength of your agreement with each statement, using a scale in which 1 denotes strong disagreement, 5 denotes strong agreement, and 2, 3, and 4 represent intermediate judgments.

There are no "right" or "wrong" answers, so select the number that most closely reflects you on each statement. Take your time and consider each statement carefully.

Strongly Disagree 1 2 3 4 5 Strongly Agree

1. When I am in a group of strangers, I am not reluctant to express my opinion publicly.
2. I find that criticism affects my self-esteem.
3. I sometimes hesitate to use my own ideas for fear they might be impractical.
4. I think society should let reason lead it to new customs and throw aside old habits or mere traditions.
5. People frequently succeed in changing my mind.
6. I find it sometimes amusing to upset the dignity of teachers, judges, and "cultured" people.
7. I like wearing a uniform because it makes me proud to be a member of the organization it represents.
8. People have sometimes called me "stuck-up."
9. Others' disagreements make me uncomfortable.
10. I do not always need to live by the rules and standards of society.
11. I am unable to express my feelings if they result in undesirable consequences.
12. Being a success in one's career means making a contribution that no one else has made.
13. It bothers me if people think I am being too unconventional.
14. I always try to follow rules.
15. If I disagree with a superior on his or her views, I usually do not keep it to myself.
16. I speak up in meetings in order to oppose those whom I feel are wrong.
17. Feeling "different" in a crowd of people makes me feel uncomfortable.
18. If I must die, let it be an unusual death rather than an ordinary death in bed.
19. I would rather be just like everyone else than be called a "freak."
20. I must admit I find it hard to work under strict rules and regulations.
21. I would rather be known for always trying new ideas than for employing well trusted methods.
22. It is better always to agree with the opinions of others than to be considered a disagreeable person.
23. I do not like to say unusual things to people.
24. I tend to express my opinions publicly, regardless of what others say.
25. As a rule, I strongly defend my own opinions.
26. I do not like to go my own way.

27. When I am with a group of people, I agree with their ideas so that no arguments will arise.
28. I tend to keep quiet in the presence of persons of higher rank, experience, etc.
29. I have been quite independent and free from family rule.
30. Whenever I take part in group activities, I am somewhat of a nonconformist.
31. In most things in life, I believe in playing it safe rather than taking a gamble.
32. It is better to break rules than always to conform with an impersonal society.

Big Five Inventory (BFI)

Here is a number of characteristics that may or may not apply to you. For example, do you agree that you are someone *who likes to spend time with others*? Please write a number next to each statement to indicate the extent to which you agree or disagree with that statement.

Disagree Strongly	Disagree a Little	Neither Agree nor Disagree	Agree a Little	Agree Strongly
1	2	3	4	5

I see myself as someone who …

1. ____ Is talkative
2. ____ Tends to find fault with others
3. ____ Does a thorough job
4. ____ Is depressed, blue
5. ____ Is original, comes up with new ideas
6. ____ Is reserved
7. ____ Is helpful and unselfish with others
8. ____ Can be somewhat careless
9. ____ Is relaxed, handles stress well
10. ____Is curious about many different things
11. ____Is full of energy
12. ____Starts quarrels with others
13. ____Is a reliable worker
14. ____Can be tense
15. ____Is ingenious, a deep thinker
16. ____Generates a lot of enthusiasm
17. ____Has a forgiving nature
18. ____Tends to be disorganized
19. ____Worries a lot
20. ____Has an active imagination
21. ____Tends to be quiet
22. ____Is generally trusting
23. ____Tends to be lazy
24. ____Is emotionally stable, not easily upset
25. ____ Is inventive
26. ____ Has an assertive personality
27. ____ Can be cold and aloof
28. ____ Perseveres until the task is finished
29. ____ Can be moody
30. ____ Values artistic, aesthetic experiences
31. ____ Is sometimes shy, inhibited
32. ____ Is considerate and kind to almost everyone
33. ____ Does things efficiently
34. ____ Remains calm in tense situations
35. ____ Prefers work that is routine
36. ____ Is outgoing, sociable
37. ____ Is sometimes rude to others
38. ____ Makes plans and follows through with them
39. ____ Gets nervous easily
40. ____ Likes to reflect, play with ideas
41. ____ Has few artistic interests
42. ____ Likes to cooperate with others
43. ____ Is easily distracted
44. ___ Is sophisticated in art, music, or literature

Fear of Pain Questionnaire-III

INSTRUCTIONS: The items listed below describe painful experiences. Please look at each item and think about how FEARFUL you are of experiencing the PAIN associated with each item. If you have never experienced the PAIN of a particular item, please answer on the basis of how FEARFUL you expect you would be if you had such an experience. Circle one rating per item to rate your FEAR OF PAIN in relation to each event.

AMOUNT OF FEAR					
Not at All	A little	A Fair Amount	Very Much	Extreme	
1	2	3	4	5	1. Being in an automobile accident
1	2	3	4	5	2. Biting your tongue while eating
1	2	3	4	5	3. Breaking your arm
1	2	3	4	5	4. Cutting your tongue licking an envelope
1	2	3	4	5	5. Having a heavy object hit you in the head
1	2	3	4	5	6. Breaking your leg
1	2	3	4	5	7. Hitting a sensitive bone in your elbow-your "funny bone"
1	2	3	4	5	8. Having a blood sample drawn with a hypodermic needle
1	2	3	4	5	9. Having someone slam a heavy car door on your hand
1	2	3	4	5	10. Falling down a flight of concrete stairs
1	2	3	4	5	11. Receiving an injection in your arm
1	2	3	4	5	12. Burning your fingers with a match
1	2	3	4	5	13. Breaking your neck
1	2	3	4	5	14. Receiving an injection in your hip/buttocks
1	2	3	4	5	15. Having a deep splinter in the sole of your foot probed and removed with tweezers
1	2	3	4	5	16. Having an eye doctor remove a foreign particle stuck in your eye
1	2	3	4	5	17. Receiving an injection in your mouth
1	2	3	4	5	18. Being burned on your face by a lit cigarette
1	2	3	4	5	19. Getting a paper-cut on your finger
1	2	3	4	5	20. Receiving stitches in your lip
1	2	3	4	5	21. Having a foot doctor remove a wart from your foot with a sharp instrument
1	2	3	4	5	22. Cutting yourself while shaving with a sharp razor
1	2	3	4	5	23. Gulping a hot drink before it has cooled
1	2	3	4	5	24. Getting strong soap in both your eyes while bathing or showering
1	2	3	4	5	25. Having a terminal illness that causes you daily pain
1	2	3	4	5	26. Having a tooth pulled
1	2	3	4	5	27. Vomiting repeatedly because of food poisoning
1	2	3	4	5	28. Having sand or dust blow into your eyes
1	2	3	4	5	29. Having one of your teeth drilled
1	2	3	4	5	30. Having a muscle cramp

Pain Catastrophising Questionnaire

Everyone experiences painful situations at some point in their lives. Such experiences may include headaches, tooth pain, joint or muscle pain. People are often exposed to situations that may cause pain such as illness, injury, dental procedures or surgery.

We are interested in the types of thoughts and feelings that you have when you are in pain. Listed below are thirteen statements describing different thoughts and feelings that may be associated with pain. Using the following scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain.

0 – not at all **1** – to a slight degree **2** – to a moderate degree **3** – to a great degree **4** – all the time

When I am in pain …

1. _____ I worry all the time about whether the pain will end.
2. _____ I feel I can't go on.
3. _____ It's terrible and I think it's never going to get any better.
4. _____ It's awful and I feel that it overwhelms me.
5. _____ I feel I can't stand it anymore.
6. _____ I become afraid that the pain will get worse.
7. _____ I keep thinking of other painful events.
8. _____ I anxiously want the pain to go away.
9. _____ I can't seem to keep it out of my mind.
10. _____ I keep thinking about how much it hurts.
11. _____ I keep thinking about how badly I want the pain to stop.
12. _____ There's nothing I can do to reduce the intensity of the pain.
13. _____ I wonder whether something serious may happen.

Appendix D: Suggestions of tailoring (algorithm)

Experimental condition

"Alright, thanks for filling those out. So, before we assign you to an intervention, we'd like to first ask you to fill a few questionnaires to be able to compute the best option of intervention for you based on your health and behavioural profile. We'll give this intervention to an algorithm that was trained on a lot of data from the UK Biobank. Have you heard of the UK Biobank? It's a data repository that collects all kinds of medical information from hundreds of thousands of people like behavioural and lifestyle information, brain scans, genetic test results, general health history, and such. It's a globally accessible repository, so data is accessible from all over the world. So, companies and organizations use this data from them to develop algorithms that can tailor treatments to people based on this data, but without needing to collect all of it, like brain scans. The algorithm that we're using is on predicting the best treatment for depression and has been trained over the past year on the full Biobank database. It takes in information about you like your sleep, your personality measures, depressive symptom constellation and general physical health, and samples which behavioural treatment, so therapies like different types of psychotherapy, light therapy, or exercise, is best for you, and then tailors the features of the intervention as well. The process should take a couple of minutes once you complete the questionnaires, depending on the number and type of variables that is used in it. So, I have a couple of extra questionnaires for you, and will need to know about your previous medical history, your sleep, and general health to be able to use the algorithm. It is completely confidential, and we will anonymize it so no identifying information like where you live, what you study, or which school you go to will be entered. Does that sound good?"

"Alright, so there is one separate consent form that you will need to fill out, this one is specific to the data that you will be providing us. It's a separate consent form specifically for the use of this algorithm that McGill asks us to get signed. I'll send you the link for that one and you will need to put your initials next to each of the statements under the information section. It's important that you read that information carefully, it's just a page. I'll send it to your email right away."

"Alright. So, you should be getting the intervention that best matches your profile in the email any moment now. Sometimes it takes up to a couple of minutes, so that's normal."

After the participant received the intervention

"So, it seems like the most effective evidence-based option for you would be a course of physical exercise, which you can do at home. Exercise is one of different treatments for depression, and there are **a lot** of studies that show its effectiveness in reducing depressive symptoms. They can be sometimes as effective as antidepressants in reducing these symptoms, and lead to large improvements in depression. In fact, medical associations in both North America and Europe are now recommending exercise as an evidence-based treatment option for mild to moderate depression. So, this plan is similar to like you would be going to a physiotherapist, who would assign you specific exercises based on your general health and some lifestyle aspects, except this is specifically for your depressive symptoms. Here are the exercises that would be good for you to do. [*Go over the intervention with them, explaining the warm-up part, the exercises for muscle training, and the aerobic exercise*. Say:] "You will need to do the warmup, these seven

exercises, so 4 sets of 15 reps each, and a set of aerobic exercise which you can do by kind of powerwalking. So, it's vigorous walking where you need to be out of breath a little bit and quite warm. You should do this outside. Sometimes it can rain, but it's important that you follow this intervention that got assigned closely for the sake of the study integrity. If you can't do some exercises because it's too much, we of course don't want you to injure yourself, but in principle you should be able to do the full set. You will need to follow these for the next two weeks. You will also get reminders to fill out some questionnaires in the meantime to make sure that we keep tracking your progress. We'd like you to follow it as best as possible. We are interested in the real-world effectiveness of this intervention, so that we can actually say if this generalizes, meaning that we'd like you to kind of tell it like it is. It's okay if you miss one or two sessions, but as long as you do most of them you'll still be able to get the 20$ on top of your 2 credits.

So that's it for today, you can start your intervention today or latest tomorrow, and then follow the schedule of either Mon-Wed-Fri, or Tue-Thu-Sat, depending on the day that you start it at. It's important that you fill out the questionnaires throughout the two weeks kind of in the same way as the first, so *before* doing the intervention sessions. It can be to the point where you fill it out right before starting.

This is the last time that we meet, actually. So, after you are done your two weeks of the intervention, you will get a final survey at the end of the study which will be slightly longer, about 15-20 minutes in total. After that one is done, you will be able to receive your credits and potentially the compensation**.** Last thing: please make sure to not share the intervention that you got with other people like your friends or family members, on the off chance that they would decide to participate in the study. We don't want them to expect to have a particular intervention before becoming part of the study."

Control condition

Great. Before we discuss the intervention that you will be following, I have some additional questionnaires for you to answer. These questionnaires are some additional personality and general health questionnaires that we'd like to control for as factors, since we have to control for a bunch of variables to match our groups.

Now before I send you these, we have an additional consent form that McGill ethics asks us to sign to make sure we cover data confidentiality in particular, given the pandemic and working online. So, I will just send you this one to read and sign, alright? You'll be getting it in your email.

Okay, your questionnaires are ready, so please take some time to answer them before we go onto the next step.

"You should be getting the email with the questionnaires. I'll be here the same way as with the previous questionnaires, so just let me know when you're done. You will get the intervention sent to your email within a couple of minutes of filling out these questionnaires."

"Alright. So you should be getting your intervention any moment now. Sometimes it takes up to a couple of minutes, so that's normal.

So your intervention for the next two weeks will be a course of exercise. Exercise is one of different treatments for depression, there are **a lot** of studies that show its effectiveness in reducing depressive symptoms, and lead to large improvements in depression. In fact, medical associations in both North America and Europe are now recommending exercise as an evidence-based treatment option for mild to moderate depression. Exercise can be sometimes as effective as antidepressants in reducing these symptoms. So, Here are the exercises that would be good for you to do. [*Go over the intervention with them, explaining the warm-up part, the exercises for muscle training, and the aerobic exercise*. Say:] "You will need to do the warmup, these seven exercises, so 4 sets of 15 reps each, and a set of aerobic exercise which you can do by kind of powerwalking. So, it's vigorous walking where you need to be out of breath a little bit and quite warm. You should do this outside. Sometimes it can rain, but it's important that you follow this intervention that got assigned closely for the sake of the study integrity. If you can't do some exercises because it's too much, we of course don't want you to injure yourself, but in principle you should be able to do the full set. You will need to follow these for the next two weeks. You will also get reminders to fill out some questionnaires in the meantime to make sure that we keep tracking your progress. We'd like you to follow it as best as possible. We are interested in the real-world effectiveness of this intervention, so that we can actually say if this generalizes, meaning that we'd like you to kind of tell it like it is. It's okay if you miss one or two sessions, but as long as you do most of them you'll still be able to get the 20$ on top of your 2 credits.

So that's it for today, you can start your intervention today or latest tomorrow, and then follow the schedule of either Mon-Wed-Fri, or Tue-Thu-Sat, depending on the day that you start it at. It's important that you fill out the questionnaires throughout the two weeks kind of in the same way as the first, so *before* doing the intervention sessions. It can be to the point where you fill it out right before starting.

Now as the last thing, we have this one questionnaire for you to fill out, it is very brief and you will get it the same way we sent you previous questionnaires.

This is the last time that we meet, actually. So, after you are done your two weeks of the intervention, you will get a final survey at the end of the study which will be slightly longer, about 15-20 minutes in total. After that one is done, you will be able to receive your credits and potentially the compensation. Last thing: please make sure to not share the intervention that you got with other people like your friends or family members, on the off chance that they would decide to participate in the study. We don't want them to expect to have a particular intervention before becoming part of the study."

Appendix E: Consent forms for tailoring

Experimental condition consent form

PLEASE READ THIS INFORMATION CAREFULLY.

The purpose of this study is to collect your information to determine which intervention would be most effective depending on your physiological and psychological profile.

We collect the data about your sleep, sleep chronotype, previous medical history in the following systems: cardiovascular, respiratory, gastrointestinal, neurological, endocrine, immune, vision, as well as allergies, medication allergies, and your overall health. This data will allow us to make extrapolations about your overall profile, potential biological markers, and resulting predispositions for particular kinds of treatments and interventions.

In this study, we are using a McGill-developed algorithm developed and trained on the data from the UK Biobank -- a large repository of health, behavioural, genetic, and neurological information from over 100 000 people. The algorithm used is 94.7% accurate in predicting the most effective treatment and uses a subset of behavioural variables that have been found to account for the most variance in treatment response.

Your data will NOT be used for any training purposes for the algorithm; it is used for this study only and will remain on a McGill server. None of this data will be shared with any third party, including any healthcare providers, the university, or other entities. Once the data is provided and the intervention/medical treatment is determined, the data will be automatically removed from any identifying information, including your name, email, phone number, location of school, and living location. Furthermore, we will have no access to any additional information beyond the one you provide us.

If you have any questions, please ask the experimenter now. If you would like to continue completing the questionnaires, please respond to each of the following questions by putting your initials next to each statement.

Control Condition consent form

PLEASE READ THIS INFORMATION CAREFULLY.

Given the unique difficulties associated with the COVID pandemic and working online, it is particularly important to emphasise data security and confidentiality. Complete confidentiality will be maintained for all those who volunteer to participate in the study. Except for this consent form and a securely stored code-key, no participant names will be recorded on any data sheets, logbooks, or computer files. Instead, each participant will be assigned a numerical code for reference. Similarly, no participant names will be mentioned in association with this work, whether presented orally or in written form in publications of any form. Only the researchers associated directly with the study and research assistants running the experiment will have access to the study material. All data will be kept in a secure file in a password-protected computer database. All data except for the code key (which will be kept for one year) will be kept for 7 years after publication of the study results, after which point it will be destroyed. A member of the McGill Review Ethics Board (REB-II), or a person designated by the McGill REB-II, may access the study data to verify the ethical conduct of this study. In addition, funding agencies and publishers often ask researchers to make their research data accessible in a trusted data repository upon completion of their study. Making research data available to others allows qualified researchers to reproduce scientific findings and stimulates exploration of existing data sets. In line with best practices in research, we will preserve the electronic data for future reuse. Upon request, data may be uploaded to a commonly used data repository (e.g., Open Science Framework). To ensure confidentiality and anonymity, the uploaded electronic data will be stripped of any information that could potentially identify the participant. Should you decide to retract your data from the study, it will be removed from our storage and destroyed; however, given that no identifying information would be associated to the data online, it would remain in the repository even if you decide to withdraw.

If you have any questions about your data security and privacy, please ask the researcher now. Otherwise, please complete the consent questions below by filling your initials next to each statement.

Appendix F: Measures Study 2

Beck Depression Inventory – II (BDI-II)

This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the one statement in each group that best describes the way you have been feeling during the past two weeks, including today. Choose the number beside the statement you have picked. If several statements in the group seem to apply equally well, choose the highest number for that group.

1. Sadness	○ 0. I do not feel sad. ○ 1. I feel sad much of the time. ○ 2. I am sad all the time. ○ 3. I am so sad or unhappy that I can't stand it.
2. Pessimism	○ 0. I am not discouraged about my future. ○ 1. I feel more discouraged about my future than I used to be. ○ 2. I do not expect things to work out for me. ○ 3. I feel my future is hopeless and will only get worse.
3. Past Failure	○ 0. I do not feel like a failure. ○ 1. I have failed more than I should have. ○ 2. As I look back, I see a lot of failures. ○ 3. I feel I am a total failure as a person.
4. Loss of Pleasure	○ 0. I get as much pleasure as I ever did from the things I enjoy. ○ 1. I don't enjoy things as much as I used to. ○ 2. I get very little pleasure from the things I used to enjoy. ○ 3. I can't get any pleasure from the things I used to enjoy.
5. Guilty Feelings	○ 0. I don't feel particularly guilty. ○ 1. I feel guilty over many things I have done or should have done. ○ 2. I feel quite guilty most of the time. ○ 3. I feel guilty all of the time.
6. Punishment Feelings	○ 0. I don't feel I am being punished. ○ 1. I feel I may be punished. ○ 2. I expect to be punished. ○ 3. I feel I am being punished.
7. Self-Dislike	○ 0. I feel the same about myself as ever. ○ 1. I have lost confidence in myself. ○ 2. I am disappointed in myself. ○ 3. I dislike myself.
8. Self-Criticalness	○ 0. I don't criticize or blame myself more than usual. ○ 1. I am more critical of myself than I used to be. ○ 2. I criticize myself for all of my faults. ○ 3. I blame myself for everything bad that happens.

9. Suicidal Thoughts or Wishes	0. I don't have any thoughts of killing myself. ○ 1. I have thoughts of killing myself, but I would not carry them out. ○ 2. I would like to kill myself. ○ 3. I would kill myself if I had the chance.
10. Crying	○ 0. I don't cry anymore than I used to. ○ 1. I cry more than I used to. ○ 2. I cry over every little thing. ○ 3. I feel like crying, but I can't.
11. Agitation	○ 0. I am no more restless or wound up than usual. ○ 1. I feel more restless or wound up than usual. ○ 2. I am so restless or agitated that it's hard to stay still. ○ 3. I am so restless or agitated that I have to keep moving or doing something.
12. Loss of Interest	○ 0. I have not lost interest in other people or activities. ○ 1. I am less interested in other people or things than before. ○ 2. I have lost most of my interest in other people or things. ○ 3. It's hard to get interested in anything.
13. Indecisiveness	○ 0. I make decisions about as well as ever. ○ 1. I find it more difficult to make decisions than usual. ○ 2. I have much greater difficulty in making decisions than I used to. ○ 3. I have trouble making any decisions.
14. Worthlessness	○ 0. I do not feel I am worthless. ○ 1. I don't consider myself as worthwhile and useful as I used to. ○ 2. I feel more worthless as compared to other people. ○ 3. I feel utterly worthless.
15. Loss of Energy	○ 0. I have as much energy as ever. ○ 1. I have less energy than I used to have. ○ 2. I don't have enough energy to do very much. ○ 3. I don't have enough energy to do anything.
16. Changes in Sleeping Pattern	○ 0. I have not experienced any change in my sleeping pattern. ○ 1a. I sleep somewhat more than usual. OR b. I sleep somewhat less than usual. ○ 2a. I sleep a lot more than usual. OR b. I sleep a lot less than usual. ○ 3a. I sleep most of the day. OR b. I wake up 1-2 hours early and can't get back to sleep.
17. Irritability	○ 0. I am no more irritable than usual. ○ 1. I am more irritable than usual. ○ 2. I am much more irritable than usual. ○ 3. I am irritable all the time.

18. Changes in Appetite	0. I have not experienced any change in my appetite. ○ 1a. My appetite is somewhat less than usual. OR b. My appetite is somewhat greater than usual. ○ 2a. My appetite is much less than before. OR b. My appetite is much greater than usual. ○ 3a. I have no appetite at all. OR b. I crave food all the time.
19. Concentration Difficulty	○ 0. I can concentrate as well as ever. ○ 1. I can't concentrate as well as usual. ○ 2. It's hard to keep my mind on anything for very long. ○ 3. I find I can't concentrate on anything.
20. Tiredness or Fatigue	○ 0. I am no more tired or fatigued than usual. ○ 1. I get more tired or fatigued more easily than usual. ○ 2. I am too tired or fatigued to do a lot of the things I used to do. ○ 3. I am too tired or fatigued to do most of the things I used to do.
21. Loss of Interest in Sex	○ 0. I have not noticed any recent change in my interest in sex. ○ 1. I am less interested in sex than I used to be. ○ 2. I am much less interested in sex now. ○ 3. I have lost interest in sex completely.

Hospital Anxiety and Depression Questionnaire (HADS)

This questionnaire is designed to help us know how you feel. Read each item and choose the option which comes closest to how you have been feeling in the past week. Don't take too long over your replies; your immediate reaction to each item will probably be more accurate than a long thought-out response.

I feel cheerful:	3. Not at all ◯ 2. Not often ◯ 1. Sometimes ◯ 0. Most of the time
I can sit at ease and feel relaxed:	◯ 0. Definitely ◯ 1. Usually ◯ 2. Not often ◯ 3. Not at all
I feel as if I am slowed down:	◯ 3. Nearly all the time ◯ 2. Very often ◯ 1. Sometimes ◯ 0. Not at all
I get a sort of frightened feeling like 'butterflies' in the stomach:	◯ 0. Not at all ◯ 1. Occasionally ◯ 2. Quite often ◯ 3. Very often
I have lost interest in my appearance:	◯ 3. Definitely ◯ 2. I don't take as much care as I should ◯ 1. I may not take quite as much care ◯ 0. I take just as much care as ever
I feel restless as I have to be on the move:	◯ 3. Very much indeed ◯ 2. Quite a lot ◯ 1. Not very much ◯ 0. Not at all
I look forward with enjoyment to things:	◯ 0. As much as I ever did ◯ 1. Rather less than I used to ◯ 2. Definitely less than I used to ◯ 3. Hardly at all
I get sudden feelings of panic:	◯ 3. Very often indeed ◯ 2. Quite often ◯ 1. Not very often ◯ 0. Not at all
I can enjoy a good book or radio or TV program:	◯ 0. Often ◯ 1. Sometimes ◯ 2. Not often ◯ 3. Very seldom

I feel tense or "wound up":	○ 3. Most of the time ○ 2. A lot of the time ○ 1. From time to time, occasionally ○ 0. Not at all
I still enjoy the things I used to enjoy:	○ 0. Definitely as much ○ 1. Not quite so much ○ 2. Only a little ○ 3. Hardly at all
I get a sort of frightened feeling as if something awful is about to happen:	○ 3. Very definitely and quite badly ○ 2. Yes but not too badly ○ 1. A little, but it doesn't worry me ○ 0. Not at all
I can laugh and see the funny side of things:	○ 0. As much as I always could ○ 1. Not quite so much now ○ 2. Definitely not so much now ○ 3. Not at all
Worrying thoughts go through my mind:	○ 3. A great deal of the time ○ 2. A lot of the time ○ 1. From time to time, but not too often ○ 0. Only occasionally

International-Positive And Negative Affect Scale-X (I-PANAS-X)

Thinking about yourself and how you normally feel, in the past week to what extent did you feel:					
	1. Never	2.	3.	4.	5. Always
Upset	○	○	○	○	○
Hostile	○	○	○	○	○
Alert	○	○	○	○	○
Ashamed	○	○	○	○	○
Inspired	○	○	○	○	○
Nervous	○	○	○	○	○
Determined	○	○	○	○	○
Attentive	○	○	○	○	○
Afraid	○	○	○	○	○
Active	○	○	○	○	○

Credibility/Expectancy Questionnaire (CEQ)

We would like you to indicate below how much you believe, right now, that the treatment you are receiving will help to reduce your depression. Belief usually has two aspects to it: (1) what one thinks will happen and (2) what one feels will happen. Sometimes these are similar; sometimes they are different. Please answer the questions below. In the first set, answer in terms of what you think. In the second set, answer in terms of what you really and truly feel.

Set I

1. At this point, how logical does the therapy offered to you seem?
○ 1. Not at all logical ○ 2. ○ 3. ○ 4. ○ 5. Somewhat logical ○ 6. ○ 7. ○ 8. ○ 9. Very logical

---

2. At this point, how successfully do you think this treatment will be in reducing your depressive symptoms?

○ 1. Not at all useful ○ 2. ○ 3. ○ 4. ○ 5. Somewhat useful ○ 6. ○ 7. ○ 8. ○ 9. Very useful

---

3. How confident would you be in recommending this treatment to a friend who experiences similar problems?

○ 1. Not at all confident ○ 2. ○ 3. ○ 4. ○ 5. Somewhat confident ○ 6. ○ 7. ○ 8. ○ 9. Very confident

---

4. By the end of the treatment period, how much improvement in your depressive symptoms do you think will occur?

○ 0% ○ 10% ○ 20% ○ 30% ○ 40% ○ 50% ○ 60% ○ 70% ○ 80% ○ 90% ○ 100 %

Set II

For this set, close your eyes for a few moments, and try to identify what you really feel about the therapy and its likely success. Then answer the following questions.

---

1. At this point, how much do you really feel that treatment will help you to reduce your depressive symptoms?

○ 1. Not at all ○ 2. ○ 3. ○ 4. ○ 5. Somewhat ○ 6. ○ 7. ○ 8. ○ 9. Very much

---

2. By the end of the treatment period, how much improvement in your depressive symptoms do you really feel will occur?

○ 0% ○10% ○20% ○30% ○40% ○50% ○60% ○70% ○80% ○90% ○ 100%