Informed Consent as a Therapeutic Intervention:

Tailoring Expectations to Maximize Recovery

Erica Michelle Abbey

Department of Psychiatry, Faculty of Medicine

McGill University, Montreal

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Abstract

Informed consent is an integral component of modern medicine; however, gaps between ethical objectives and psychological corollaries linger. Despite mounting evidence to demonstrate its impact on human behavior, physicians and bioethicists scantily construe it as a source of therapeutic influence. Here we explore judicious ways to leverage this standard-of-care tool as both an ethical requisite in the clinical milieu and a procedure, which could either bolster or deflate the health of individuals, perhaps through a placebo effect.

First, in a literature review, we examine the history and components of the informed consent process, and its relation to bioethical principles and patient-practitioner models. We explore relevant psychological mechanisms, such as the placebo and nocebo effect, that are inherent in consent discussions as well as in clinical practice. Applying this information, we offer an attractive recommendation that not only harmonizes the sometimes-clashing bioethical principles of autonomy and non-malfeasance, but also serves as an intervention to improve therapeutic outcome. Further, the review explains the ethical concerns embedded in placebo use, such as deception, abuse of trust, and manipulation, and shows how using the informed consent to elicit a placebo effect withstands ethical scrutiny.

Second, we investigate if the informed consent process may actually function as a therapeutic, autonomous intervention. We tested if suggestions given during the informed consent procedure could elicit a placebo effect that would influence the postoperative experience of patients undergoing third molar extractions. Results from this randomized controlled pilot study at the Jewish General Hospital in Montreal indicated that slightly modifying consent form information and tenor decreased overall symptom severity scores on the Postoperative Symptom Severity Scale for experimental subjects compared to controls, as well as overall pain scores on the McGill Pain Questionnaire. Our findings suggest that altering expectations during the informed consent discussion may minimize manifested symptoms experienced post-surgically.

Lastly, we study the risk factors often considered to influence postoperative recovery following third molar extractions. The analysis included patients' preoperative expectations as a determinant for the severity of postsurgical pain. Standardized coefficients demonstrated that out of age, gender, number of teeth removed, difficulty of extraction, operation time, intervention, and patient expectations, the latter was the largest significant predictor of postoperative pain scores. These results demonstrate that preoperative expectations are of utmost importance when predicting and determining the severity of patient recovery.

Résumé

Bien que le consentement éclairé soit une partie intégrante de la médecine contemporaine, un fossé entre les objectifs éthiques et les connaissances psychologiques demeure présent. En effet, malgré l'accumulation de preuves scientifiques démontrant l'influence du formulaire de consentement sur le comportement humain, les médecins et bioéthiciens considèrent rarement ce dernier comme ayant un impact thérapeutique. Nous explorons ici la possibilité de percevoir cette norme de diligence comme étant à la fois une obligation éthique du milieu clinique et une procédure thérapeutique pouvant, probablement par le biais d'un effet placebo, aider ou nuire à la santé de l'individu.

En premier lieu, dans une revue de la littérature nous examinons l'historique et les composantes du processus de consentement éclairé et étudions comment ce dernier correspond aux principes de la bioéthique et aux modèles de relation entre les patients et les professionnels de la santé. Nous explorerons également les mécanismes psychologiques importants dans le processus de consentement et dans la pratique clinique, comme par exemple les effets placebo et nocebo. Mettant en pratique cette information, nous proposons une attirante suggestion dans l'utilisation du processus de consentement éclairé qui promet de rééquilibrer l'harmonie entre les principes éthiques d'autonomie et de non-malfaisance, lesquels ont tendance à s'affronter dans l'utilisation traditionnelle de ce processus. Notre suggestion servira également d'intervention qui aidera au processus de guérison. Enfin, la revue littéraire expliquera les préoccupations éthiques comprises dans l'utilisation des placebos, comme par exemple la déception, l'abus de confiance et la manipulation, puis détaillera en quoi l'utilisation de l'effet placebo dans le processus de consentement contrebat ces problèmes éthiques.

En second lieu, nous cherchons à savoir si le processus de consentement éclairé peut effectivement fonctionner comme une intervention thérapeutique autonome. Plus précisément, nous avons testé si des suggestions administrées au cours du processus de consentement peuvent produire un effet placebo influençant l'expérience thérapeutique de patients suite à l'extraction chirurgicale des troisièmes

molaires. Nous avons menée cette étude à l'Hôpital Général Juif de Montréal et avons utilisé un échantillonnage aléatoire afin de s'assurer de la validité des résultats. Les résultats de cette étude pilote indiquent qu'une légère modification de l'information et de la teneur générale du formulaire de consentement suffit pour réduire la sévérité des symptômes évalués sur l'échelle de sévérité des symptômes postopératoires [Postoperative Symptom Severity Scale], ainsi que pour réduire les indices de douleur du Questionnaire sur la douleur de McGill [McGill Pain Questionnaire]. En effet, nos résultats démontrent qu'une modification des attentes des patients lors du processus de consentement peut éliminer, ou du moins réduire, les symptômes reliés à l'expérience postopératoire.

Finalement, nous étudions les facteurs de risque souvent considérés comme ayant un impact sur la guérison suite à l'extraction chirurgicale d'une troisième molaire. L'analyse incluait les attentes des patients concernant la sévérité des symptômes post-chirurgicaux. Des coefficients standardisés ont indiqué que, parmi les variables étudiées (âge, sexe, nombre de dents extraites, difficulté de l'extraction, temps d'opération, intervention et attentes des patients), les attentes des patients sont les meilleurs prédicteurs des résultats postopératoires. Ces résultats démontrent l'importance des attentes préopératoires sur la prédiction des symptômes et de leur sévérité chez des patients en rémission chirurgicale.

Preface

Contributions of Authors

Three original manuscripts constitute the present thesis. I authored the first manuscript entitled *Informed Consent as a Therapeutic Intervention: Reconciling Autonomy and Non-Malfeasance through a Placebo Effect*. Dr. Allan Lisbona, Dr. Mel Schwartz, Dr. Amir Raz, and myself authored the second and third manuscripts, entitled *Effects of the Consent Form: Using Wisdom Teeth Extractions as a Lens* and *Expectation as a Determinant of Pain following Removal of Third Molars*. All authors contributed to the development of the methodology and select interpretation of results. Dr. Lisbona performed the third molar extractions. I collected, analyzed and interpreted the data, and drafted the manuscripts. All authors will read, edit and approve the final versions before submission for publication.

Thesis Objectives and Rationale

Through a multidisciplinary approach combining psychology, bioethics, and dentistry, this manuscript-based thesis aims to understand the effects expectation can have on therapeutic outcome. With mounting evidence demonstrating that informed consent cultivates negative expectations that may lead to symptom worsening, it follows that a dilemma may occur between patient autonomy and a physician's duty to do no harm. In a literary review, we first deconstruct this standard-of-care tool to understand its origins, intentions and implications, and subsequently offer a recommendation to transform informed consent into a process that dually serves as an ethical requisite as well as a therapeutic intervention. We then test this recommendation in the dental field, using wisdom teeth extractions as a lens. Further, we explore the risk factors of post-extraction pain, primarily focusing on the importance of preoperative expectations in determining pain severity. We believe that the findings from this body of work will provide new insights into the seemingly neutral process of obtaining informed consent, which may have profound implications for current healthcare.

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Informed Consent as a Therapeutic Intervention: Reconciling Autonomy and Non-Malfeasance through a Placebo Effect

Erica Abbey[1]

[1]Department of Psychiatry, Faculty of Medicine, McGill University, Montreal, Canada

Abstract

Informed consent is a universally acclaimed bioethical ideal, yet proponents striving for this form of patient autonomy generally neglect to consider its therapeutic consequences, especially those that undermine the principle of non-malfeasance. Granting informed consent – by reading a form or listening to a detailed explanation – provides individuals with information that will likely guide expectations and shape clinical outcome. Research has shown that the disclosure of side effects may inadvertently increase potential harm to the individual by creating suggestions and garnering expectations that symptoms are likely to occur, otherwise known as a nocebo effect. To address this concern, the current review proposes that the tension between balancing autonomy with non-malfeasance might be resolved by using these same psychological processes to elicit a placebo effect. The informed consent process may therefore actually serve as an autonomous intervention. Here, through a literary review, we explore judicious ways to leverage this standard-of-care tool as both an ethical requisite in the clinical milieu and as a preoperative intervention, by considering its history, components, and psychological implications, as well as the ethical concerns embedded in placebo use.

Keywords: Informed Consent, Autonomy, Non-Malfeasance, Intervention, Nocebo Effect, Placebo Effect

Introduction

Informed consent is as an integral component of modern medicine. Grounded in the ethical principle of autonomy, where every competent person has the right to make informed decisions about the medical treatment they receive, it is now customary to fully disclose the risks, benefits and alternate options associated with any clinical procedure (Collier & Haliburton, 2011). Unfortunately, in the very process of describing the risks, physicians may induce iatrogenic harm in the form of a nocebo (negative placebo) effect, whereby the patient's expectation of side effects actually causes those side effects to occur (Wells & Kaptchuk, 2012; Benedetti, Lanotte, Lopiano, & Colloca, 2007).

Causing harm through the informed consent process denotes a discord between bioethical principles. On the one hand, withholding information undermines autonomy. On the other hand, providing full disclosure of possible symptoms jeopardizes the maxim of non-malfeasance – a physician's duty to do no harm (R. Wells & Kaptchuk, 2012). Thus, the question arises: how can information be relayed to the patient while respecting both principles?

An investigation into the positive and negative consequential psychosocial processes implicated in informed consent may help attenuate this dilemma. Research supports that understanding the concepts behind the nocebo effect and the power of suggestion may help defend against the manifestation of these effects (Fries & Loftus, 1979). We can therefore structure the informed consent process to serve as an autonomous intervention that will influence the therapeutic outcome in a beneficial way. We believe that such a strategy upholds patient autonomy while satisfying the physician's need to balance informed consent and non-malfeasance.

To explore the intricacies involved in informed consent, this paper examines the history and components of the process, and its relation to bioethical principles and patient-practitioner models. It explores relevant psychological mechanisms, such as the placebo and nocebo effect, that are inherent in consent

discussions as well as in clinical practice. Applying this information, we offer an attractive recommendation that not only harmonizes the sometimes-clashing bioethical principles of autonomy and non-malfeasance, but also serves as an intervention to improve therapeutic outcome. Further, the review considers the ethical concerns embedded in placebo use, such as deception, trust, and manipulation, and shows how using the informed consent to elicit a placebo effect withstands ethical scrutiny.

Informed Consent

The History of Informed Consent

While the concept of "consent" has been well established since the turn of the century, "informed consent" only rose to prominence after World War II. In response to the abusive treatment and horrific medical experiments Nazi physicians performed on prisoners, the Nuremberg Code of 1947 – 10 strict principles meant to govern all medical research using human subjects – emerged (Corrigan, 2003). The first principle, which soon became one of the primary ethical considerations in all biomedical research, stipulated that 'the voluntary consent of the human subject is absolutely essential'(Annas & Grodin, 1992). It further maintained that all risks involved must be disclosed, in detail, regardless of the psychological impact the disclosure may have on the individual. Researchers and physicians, however, viewed the Nuremberg Code as rigid and unrealistic, therefore triggering the development of the Declaration of Helsinki. This more flexible doctrine indicated that practitioners should obtain the patient's freely given consent if possible (Bray, Shepherd, & Ray Hays, 1985), and it allowed physicians to withhold information from their patients under the principle of therapeutic privilege (Collier & Haliburton, 2011). Despite these less restrictive regulations, informed consent did not initially become routine practice (Corrigan, 2003).

In 1957, the California Court of Appeals in *Salgo v Leland Stanford Jr. University Board of Trustees* directly addressed this issue. Following a translumbar aortography, the plaintiff was paralyzed in his lower extremities. The plaintiff's primary claim was negligent failure to provide information about the risks of the procedure. Although the appeals court reversed the decision in favor of the physician, the court recognized, for the first time, that physicians might be held liable for failure to provide pertinent and sufficient information to their patients (Fries & Loftus, 1979). This acknowledgement provided the backbone of the informed consent model seen today.

In more recent times, different legal standards have been developed concerning the amount of information relayed during the informed consent procedure. The "reasonable *physician* standard" acknowledges that adequate information relies on what a typical physician would say about the intervention. Inevitably, this permits the physician to determine what information is appropriate to share. The "reasonable *patient* standard", on the other hand, insists on providing sufficient information to the patients so that they can participate in the decision-making process (Beirne, 2011). The physician contributes information about the diagnosis, prognosis, and treatment options, including risks and benefits, and often provides a medical opinion as well as a treatment recommendation. Patients impart their unique set of preferences, values, and health care goals through which they interpret the treatment recommendation (Bernat & Peterson, 2006).

Patient–Practitioner Relationship in Decision-Making

Compared to the preceding 25 centuries, interactions between a healthcare provider and patient have drastically changed over the past four decades (Papakostas & Daras, 2001). In the past, medical paternalism prevailed. Adopting a paternalistic role, practitioners implicitly kept the patient's interests in mind while primarily focusing on the disease or condition, giving little attention to the patient's concerns or beliefs (Barr & Threlkeld, 2000). That

meant that patients, without question or doubt, were expected to comply with the doctor's instructions (Herring, 2009). An underlying assumption was that the patient's acceptance of the advice would improve or ensure a positive outcome, whereas the patient's rejection of the advice might compromise health or recovery (Barr & Threlkeld, 2000).

The paternalistic model postulates that both practitioner and patient share the same objective criteria in determining what promotes the patient's health and well-being. For this reason, the physician can presumably discern what is in the patient's best interest with limited patient participation. Ultimately, it is believed that patients will be thankful for these decisions even if they would not have agreed with them in the first place (Emanuel & Emanuel, 1992). In the tension between the patient's autonomy and well-being – between choice and health – the paternalistic physician's main emphasis is toward the latter. Patient autonomy is perceived as patient assent; the physician is the patient's guardian, articulating and implementing what is perceived to be best (Emanuel & Emanuel, 1992).

The encounter today can no longer be seen as this kind of parent–child relationship, but rather as one between two morally autonomous agents. Depicted as an antidote to counter medical paternalism, the informed consent process endorses the empowered, informed, and autonomous decision-making patient (Corrigan, 2003). In this informative-type model the physician provides the patient with all relevant information, the patient selects the medical intervention they want, and the physician carries out the selected intervention. The physician is a purveyor of technical expertise. He has important obligations to provide truthful information to the patient, to maintain competence in his area of expertise, and to consult others when his knowledge or skills are lacking (Emanuel & Emanuel, 1992).

In the tension between the patient's autonomy and well-being, the physician's main emphasis is toward the former. Patient autonomy is perceived as patient choice over medical decision-making; the physician provides the means for the patient to exercise control (Emanuel & Emanuel, 1992).

A common misconception is that informed consent is a one-time event. In fact, it is best viewed as a process or an ongoing dialogue between the patient and health care practitioner with an end goal of mutual understanding. While the practitioner tries to understand the patient's health objectives, expectations, and fears, the patient tries to grasp what the treatment involves, how it matters to the their wellbeing, and how it will affect their life in the short and long term (Bernat & Peterson, 2006). Together, patients and physicians agree on a treatment regime that can then be carried out, and reevaluated along the way (Marzuk, 1985; Whitney, McGuire, & McCullough, 2004). This shared decision-making model characterizes the best integration of physician expertise and patient choice (Bernat & Peterson, 2006)

Patient Perceptions of Informed Consent

There is strong evidence to demonstrate that patients are satisfied with their health care experience when they are supplied with and understand information about their diagnosis, treatment, and clinical advice (Humphris, O'Neill, & Field, 1993). A study by Degerliyurt, Gunsolley, & Laskin (2010) showed that most patients (57%) want to know about all the possible complications of treatment, and 78% want written information; only a small percentage (7%- 10%) of patients did not want to receive information about complications. Similarly, a study by Ferrus-Torres, Valmaseda-Castellon, Berini-Aytes, & Gay-Escoda (2011) found that 96% of patients were in favor of being given information before undergoing surgery.

Informed consent may be explored throughout many health care settings, with the dental practice being an ideal backdrop for such research. In a qualitative study by King (2001), people described different ways in which they received information when visiting the dentist. 'It was all verbal information, it was the dentist explaining what was needed next and in very simple terms really, in this particular case it was a replacement crown so he was saying you need one

because and explained why' (Christopher in King, 2001). Although some respondents felt that they had received sufficient information, others felt ill informed about their treatment. 'I was very naive about it, what the terms were even. I was not even sure what I had fitted. There wasn't much discussion ...there were definitely no leaflets or plan or anything like that.' (Carol in King, 2001) Treatment was not always well explained or options discussed. 'I didn't know anything about it. It would be nice to know what I was actually having done or whether there were alternative treatments' (John in King, 2001).

In the study by Ferrus-Torres et al. (2011), patients were asked open and directed questions to investigate their perceptions of the informed consent process. When asked what they consider to be the function of informed consent, the three prevailing answers included: to explain the possible complications of the surgical operation; to explain the possible complications of the operation and to obtain patient consent for the surgery; and to agree to proceed with the surgery despite the possible complications. When the patients were asked for their opinion on receiving information on the possible complications, the majority (59%) thought it was necessary, while 30% reported feeling more afraid and 7% believed they were more nervous. When asked if the postoperative symptoms occurred as described preoperatively, 71% replied that the postoperative period was very similar to what had been explained before surgery (Ferrus-Torres, Valmaseda-Castellon, Berini-Aytes, & Gay-Escoda, 2011). These findings become quite interesting when considering the psychological perspectives of an informed consent discussion, which will be discussed later on in this review.

Components of Informed Consent

Current bioethical theory deconstructs the process of informed consent into three components: disclosure, capacity, and voluntariness.

Disclosure refers to "the provision of relevant information by the clinician and its comprehension by the patient" (Etchells, Sharpe, Walsh, Williams, & Singer, 1996). To ensure its integrity, physicians and researchers are expected to uphold certain requirements: first, they should inform the patient of their disease state, the nature of possible diagnostic and therapeutic interventions, the nature and probability of risks and benefits associated with the proposed intervention, as well as alternatives, and any uncertainties of knowledge (Emanuel & Emanuel, 1992). Second, they ought not lie to the patient nor withhold information that the patient may find important in making a decision. Lastly, they should make an effort to determine whether or not the patient understands the information (Collier & Haliburton, 2011).

Capacity refers to the patient's ability to understand the relevant information and to realize the foreseeable consequences of their decision. Capacity in this context can be defined as possessing the mental, emotional, and physical capabilities needed to be competent in giving informed consent (Friedman, Felten, & Millett, 2000). Children, the senile, the comatose, and participants in research involving deception, for example, are presumed to lack this inner freedom to make a truly informed decision (Bray et al., 1985).

Voluntariness refers to the "patient's right to come to a decision freely, without force, coercion or manipulation" (Etchells et al., 1996). Moreover, the patient has the right to refuse treatment, a decision respected even more than the right to demand it. This reflects the notion that having treatment forced upon oneself is a greater offence to one's autonomy than not being able to have the desired therapy. If a patient with capacity refuses to consent to treatment, it would be unlawful to provide it; contrarily, if a patient demands a particular treatment, the doctor is entitled to refuse to give it, if the doctor decides it is not appropriate (Herring, 2009).

Bioethics and Informed Consent

The complexities behind the patient–physician relationship, including the need to develop an acceptable doctrine of conduct, resulted in the promulgation of four principles that eventually became the foundation of bioethics: (1) *autonomy*, referring to the right of an individual to determine what will be done to his or her mind and body; (2) *beneficence*, reflecting the duty to promote good and minimize harm; (3) *non-malfeasance*, upholding the duty to do no harm; and (4) *justice*, meaning a fair and equitable distribution of health care resources (Collier & Haliburton, 2011; Fries & Loftus, 1979).

The contents of this paper primarily focus on two of the four principles: autonomy and non-malfeasance.

Autonomy

Autonomy, broadly characterized, embodies the concepts of self-determination and freedom (Monagle & Thomasma, 2004). In bioethics, the principle holds that people have the right to be free agents who can make their own decisions about treatment. It is based on the premise that people have, or should have, control over what is done to their bodies (Collier & Haliburton, 2011). To quote from moral philosophers Tom Beauchamp and James Childress's influential biomedical ethics text:

> "… the core idea of personal autonomy is an extension of political self-rule to self-governance by the individual: personal rule of the self while remaining free from both controlling interferences by others and personal limitations such as inadequate understanding that prevent meaningful choice" (Beauchamp & Childress, 2001).

Non-Malfeasance

The principle of non-malfeasance asserts that medical professionals should not harm their patients (Gillon, 1994). Founded in the Hippocratic Oath – a declaration of ethical standards for doctors that dates back to the fifth century BC

– it recounts: "I will use treatment to help the sick according to my ability and judgment, but I will never use it to injure or wrong them" (Herring, 2009). This is otherwise known as the maxim *primum non nocere: 'first, do no harm.'*

At first glance, it seems that autonomy and non-malfeasance work in tandem with one another. But what happens when they fall out of harmony, when the practice of one undermines the other? The issue becomes more complicated than initially thought; it is possible that the disclosure of details during the informed consent process may inadvertently cause iatrogenic harm to the patient. We will now elaborate on this matter by considering evidence from psychological research about placebo and nocebo effects. We then offer a potential resolution that mutually respects both of these conflicting principles.

Psychological Perspectives

The Placebo and Nocebo Effect

The responses of human beings to information are intricate. Plying a person with certain kinds of information can alter attitudes, thoughts, emotions, behaviors, and memories (Loftus, 1979, 2005). Acting as a suggestion, it can lead people to experience feelings and symptoms that they would not otherwise feel (Barsky, Saintfort, Rogers, & Borus, 2002; Beecher, 1955; Flaten, 1998; Hahn, 1997; Shapiro & Morris, 1978). Many compelling assays demonstrate the power of suggestion. For instance, being told that they were ingesting alcohol, participants in a psychology experiment showed symptoms of alcohol intoxication even when consuming nonalcoholic beverages (Marlatt & Rohsenow, 1981). In another study, researchers instilled specific food-avoidance behaviors in adults by repeatedly suggesting that the subjects had become ill from eating the particular foods in childhood (Bernstein, Laney, Morris, & Loftus, 2005). These studies provide a sampling of the diverse influence suggestion can wield on physical and mental experience.

Similar effects have been reported in cardiovascular, immune, and hormone system disorders, pain, (anti-) depression, anxiety, Parkinson's, asthma, (anti-) migraine, and many other conditions (for reviews see Benedetti, 2008, 2010; Kirsch et al., 2008; Lewis, Winner, & Wasiewski, 2005; Moerman, 2002; Moncrieff, Wessely, & Hardy, 2004; Oken, 2008; Wampold, Minami, Tierney, Baskin, & Bhati, 2005). These cases exemplify the phenomenon known as the placebo (and nocebo) effect. The archetypal placebo effect is defined as a desirable outcome, where patients experience a healing effect because they attach positive meanings and emotions to a treatment. In pain studies, the term is denoted as placebo analgesia. In contrast, the nocebo effect occurs when patients cultivate negative meanings and emotions (Papakostas & Daras, 2001). Belief is central to the phenomena; one's belief of improvement results in healing whereas one's belief of worsening resulting in deterioration (R. E. Wells, 2012). Nocebo ("I shall harm") was introduced in contraposition to the term placebo ("I shall please") to facilitate the distinction between the beneficial and the noxious effects of placebo use (Enck, Benedetti, & Schedlowski, 2008; Hahn, 1997; Kennedy, 1961).

The term placebo initially referred to biologically inert substances used in pharmacological research, where active chemical agents were compared with pharmacologically inactive ones (e.g. a sugar pill) (Lundh, 1987). The inactive pill, because it lacked a specific pharmacologic effect, acted therapeutically through its "symbolic power" and its impact on the patient's imagination, beliefs, expectations, and emotions (Papakostas & Daras, 2001). The focus is now being shifted from "inert compound" to the concept of a nonspecific therapy that can be driven by many different aspects – comprised of the individual patient, the clinician, and the interaction between the patient, clinician and treatment environment (Finniss, Kaptchuk, Miller, & Benedetti, 2010). According to Shapiro & Morris (1978),

> "A placebo is defined as any therapy or component of therapy that is deliberately used for its psychologic[al], physiologic[al], or psycho-physiologic[al] effect of any medication or procedure given with

therapeutic intent which is independent of or minimally related to the effects of the medication or to the specific effects of the procedure and which operates through a psychologic[al] mechanism."

Theories of the Placebo and Nocebo Effect

Typically treated as competing perspective, the two main approaches that address the placebo and nocebo experience are classical conditioning and the expectancy theory.

The Classical Conditioning Theory

Classical conditioning is a learning process in which a stimulus initially incapable of evoking a response acquires the ability to do so. This occurs through repeated pairings with another stimulus that is already able to elicit the desired response. According to this view, active treatments are unconditioned stimuli (US), and the vehicles in which they are delivered (e.g., pills, surgery, etc) are conditioned stimuli (CS). Through US- CS pairings, the vehicles come to elicit the effects of active therapies, even in the absence of the latter. This is characterized as a conditioned response (CR). In a medical context, active treatments (US) elicit beneficial effects (unconditioned response, UR). Pairing an active treatment with the act of receiving treatment (CS) conditions patients to experience the beneficial effects from the CS alone. The important point here is that the act of receiving treatment becomes independent of whether the treatment is active or inactive. Therefore, receiving an inert pill or undergoing a sham procedure will consequently elicit the therapeutic effects because it has been conditioned to do so (Kirsch, 1985, 1997).

There are, however, inconsistencies in this model, especially pertaining to extinction. Extinction in classical conditioning refers to the elimination of the conditioned response after long-term absence of the US-CS pairings. In a study by Montgomery (1995), the placebo effect actually increased over the course of 10 extinction trials, with contradicts the classical conditioning model. In another study by Coryell & Noyes (1998), placebo treatment for panic disorder retained

its effectiveness during an 8-week period of daily placebo administration (Coryell & Noyes, 1988). This indicates that classical conditioning alone cannot sufficiently explain placebo phenomena.

The Expectancy Theory

The expectancy theory embodies a common understanding of the placebo effect: a placebo produces an effect because the recipient expects it to. That is, the placebo treatment elicits an expectation for a particular effect, and the expectation produces that effect (Stewart-Williams & Podd, 2004). According to Kirsch (1997), for example, the expectation of depression directly causes depression, and the expectation of anxiety directly causes anxiety (Kirsch, 1997). The model also implies, for instance, that the expectation of pain relief is pain relieving (Stewart-Williams & Podd, 2004).

How, though, do expectancies produce placebo effects? In a review by Stewart-Williams & Podd (2004), several accounts are offered. One hypothesis is that expectancy effects are a product of anxiety reduction (Lundh, 2000). Thinking that one will get better after receiving treatment may lead to a reduction in anxiety, which may in turn boost immune system functioning (Turner, Deyo, Loeser, Von Korff, & Fordyce, 1994). Another hypothesis is that expectancy effects may be mediated by changes in other cognitions; the expectation of analgesia may increase the frequency of coping cognitions, which may in turn lessen the experience of pain (Peck & Coleman, 1991; Spanos, Perlini, & Robertson, 1989). A further possibility is that changes in expectancy produce changes in behavior, and new behavior directly influences health outcomes (Bootzin, 1985; Turner et al., 1994). For example, patients in pain who are expecting improvement may resume normal daily activities, which may lead to improved mood and distraction from pain. These factors may help in the reduction of pain experience (Peck & Coleman, 1991; Stewart-Williams & Podd, 2004).

Neurobiology of the Placebo and Nocebo Effect

Elucidating the underlying neurobiology of placebo and nocebo effects can further our scientific understanding of these mechanisms (Benedetti, 2010; Oken, 2008). However, it may be difficult to rely on reductionism alone to explain such intricacies. For instance, biological models appear unable to fully explain why placebo injections work better than pills (De Craen, Tijssen, De Gans, & Kleijnen, 2000); why blue inert pills mellow, while red ones stimulate (De Craen, Roos, De Vries, & Kleijnen, 1996); why four placebos work better than two (De Craen et al., 1999); why more expensive placebos work better than cheaper ones (Waber, Shiv, Carmon, & Ariely, 2008); or why a placebo thought to be morphine acts like morphine whereas a placebo thought to be aspirin acts like aspirin (Kihlstrom, 2003). The wide-range of phenomena renders it unlikely that there exists a single placebo/nocebo effect (Benedetti, 2010; Kaptchuk et al., 2008; Miller & Kaptchuk, 2008), but just how much these effects operate via similar mechanisms is unclear.

Nonetheless, the past decade has seen an explosion of studies using positron emission tomography (PET), functional magnetic resonance imaging (fMRI), electroencephalography (EEG), and magnetoelectroencephalography (MEG) in humans to understand the neural bases for these placebo and nocebo effects (Tracey, 2010).

Studies exploring the neural basis of pain and its relief via pharmacological and psychological means have contributed substantially to our knowledge of placebo analgesia. Several brain areas – termed the pain matrix – show increased activity, often bilaterally, when humans experience pain (e.g. Apkarian, Bushnell, Treede, & Zubieta, 2005; Tracey & Mantyh, 2007). During analgesia induced via pharmacological or psychological interventions, decreased activity of this 'pain matrix' is often observed (Tracey, 2010). In fMRI experiments published by Wager et al. (2004), they found that pain-related neural activity was reduced within the thalamus, anterior insular cortex, and anterior cingulate cortex during the placebo condition compared to baseline. In addition, the magnitudes

of these neural activity decreases were correlated with reductions in pain ratings (Price, Finniss, & Benedetti, 2008).

Placebo analgesia, furthermore, is often associated with the release of endorphins in the brain (Stewart-Williams & Podd, 2004**)**. It was first shown that placebo analgesia could be blocked by the opioid antagonist naloxone, which supported the involvement of endogenous opioids (Levine, Gordon, Smith, & Fields, 1981). Several subsequent studies confirmed and extended this observation. For example, in an experimental model of pain, Amanzio and Benedetti (1999) demonstrated that naloxone blocked the placebo response if it was induced by strong expectation cues, whereas if the expectation cues were reduced, it was insensitive to naloxone. These data show the complexity behind placebo analgesia processes, wherein various mechanisms come into play under different circumstances (Benedetti, Mayberg, Wager, Stohler, & Zubieta, 2005), or not at all.

Brain-imaging techniques have also been fundamental in the understanding of nocebo effects. Negative information given verbally has been shown to convert typically painless stimulations into pain (e.g. Colloca, Sigaudo, & Benedetti, 2008; Rodriguez-Raecke et al., 2010). In one study, when subjects were told that drug infusion was stopped (even though it was not) the brain's analgesic effects induced by μ-opioid agonist remifentanil were completely overridden. This suggests that negative expectations may interfere with the drug's pharmacodynamic profile (Bingel et al., 2011; Tracey, 2010). In a recent study by Shelke et al. (2008), it was found that the level of expected pain influenced perceived pain. Participants viewed high and low-intensity visual cues followed by noxious thermal stimuli. By comparing the brain activations produced by the visual cues, significant differences in the ipsilateral caudal anterior cingulate cortex, head of the caudate, cerebellum and contralateral nucleus cuneiformis were found (Colloca & Miller, 2011). Overall, these experimental findings in the field of pain have relevance for other clinical

situations where mental processes act as a major factor affecting medical outcomes.

Nocebo Effects and Informed Consent

Noticing the power of the spoken word when the physician's information and the patient's suggestibility interact, researchers started investigating patients' responses to full disclosure of possible side effects. In early work by Loftus and Fries (1979), subjects who participated in a drug trial underwent a standard informed consent procedure, including an overview of potential side effects. Many of those given a saline injection, i.e. a placebo injection, reported the discussed symptoms, such as nausea, vomiting, dizziness, and even mental depression. This offers preliminary evidence that informing patients about side effects may act as a suggestion that they are likely to occur, therefore creating the expectation and potential for manifestation even when an inert compound is given (Loftus, 1979).

The literature has not been able to conclusively determine whether forewarning patients of side effects influences the incidence of those side effects. Whereas some researchers propose that informing patients of side effects causes no harm (e.g. Howland, Baker, & Poe, 1990; Ley, 1982; E. D. Myers & Calvert, 1973), many others tend to disagree (e.g. Wells & Kaptchuk, 2012; Colloca & Finniss, 2012; Colloca & Miller, 2011; Loftus & Fries, 2008; Mondaini et al., 2007; M. G. Myers, Cairns, & Singer, 1987; Silvestri et al., 2003). Myers et al (1987) noted a compelling example from a multicenter, placebo-controlled trial of aspirin treatment for unstable angina. In their study (n=555), the consent form at two of the participating centers specifically listed "gastrointestinal irritation" as a possible side effect, while the consent form at the third center did not. Patients at the former institutions reported significantly higher incidences of gastrointestinal symptoms ($p<0.001$) and were more likely to withdraw from the study because of gastrointestinal distress ($p<0.001$) (M. G. Myers et al., 1987).

A study by Silvestri et al. (2003) examined the presence of erectile dysfunction (ED) in adults using beta-blockers for cardiovascular disease (n=96). In the first phase, all participants received atenolol, a drug known to induce ED. The group not informed about the drug's side effects had the least incidence of ED (3.1%). Those only told the name of the drug had a 15.6% incidence of ED, while those advised about both the name and symptom profile of the beta-blocker reported the highest incidence of ED (31.2%). In the second phase, all patients who had reported ED were randomized to receive Sildenafil citrate (i.e. Viagra, a treatment for ED) or a placebo in a cross over study. Sildenafil citrate and placebo were equally effective, with the exception of one patient, in reversing erectile dysfunction (Silvestri et al., 2003). This example supports the notion that the disclosure of details during the informed consent process can elicit a nocebo effect, which resultantly hinders the patient's therapeutic outcome. Interestingly, a placebo effect was able to reverse the negative results.

Researchers propose that an explanation to the increased reporting of negative symptoms may be that patients feel more comfortable or justified in mentioning a symptom if they know it is an appropriate side effect. Otherwise, they might be embarrassed to declare it or assume it has nothing to do with treatment (Hrobjartsson & Gotzsche, 2001; Hrobjartsson, Kaptchuk, & Miller, 2011). It is important to keep in mind, however, that patients who receive a placebo treatment – a treatment that is pharmacologically inert – still report side, or even main effects that have been mentioned to them during the consent process. Even if patients feel more comfortable or justified, it stands that they should not have experienced the side (or main) effects in the first place. Moreover, expectations can also induce symptoms in healthy non-patients (Barsky et al., 2002). Volunteers, being told, for example, that a (nonexistent) headache-inducing mild electric current would be passed through their heads, reported experiencing headaches (Schweiger & Parducci, 1981). This supports the overarching message that expectation, and therefore disclosure of information, have the ability to actually alter experience.

Informed Consent as an Intervention

The Problem

Predicaments arise when two (or more) key ethical principles conflict with and violate one another. In the following hypothetical situation similar to one proposed by Wells & Kaptchuk (2012), let us consider the discord between autonomy and non-malfeasance: for patient A, the physician recommends a procedure and describes all of the potential side effects. For patient B, the physician tailors the information to only include some of the side effects of the same procedure. Patient B hardly develops any symptoms, while patient A develops a multitude of them.

Although patient A was fully informed about the side effects, the disclosure itself played a part in their manifestation. Accordingly, the patient's autonomy was respected, but the principle of non-malfeasance was violated. In the case of patient B, autonomy was hindered yet the patient had a more desirable outcome, adhering to the standard of non-malfeasance. At first glance, it seems that there is no clear-cut resolution as to how a health care practitioner should proceed without prioritizing one principle over the other.

The Solution

By taking into account the psychological phenomena previously discussed, we can structure the informed consent process to serve as an autonomous intervention that will influence outcome in a beneficial way. Literature indicates that just as expectations of possible symptoms can cause those symptoms to occur, understanding placebo and nocebo effects and the power of expectations can defend against those effects. In an unpublished pilot study with scleroderma patients at the Stanford University Medical School, Loftus and Fries (2008) incorporated a special message into the informed consent discussion explaining the powerful role that expectations can play in producing unlikely symptoms. It read as follows:

> "You should keep in mind one important point about these possible side effects. Research has shown that simply mentioning possible annoying symptoms causes some people to experience these symptoms – even when no drug is taken at all. This happens because mention of the symptoms causes some people to expect that they will experience them, and a person's expectations can then lead to the actual experience. Very few people will actually have these problems and you can help yourself guard against these sorts of discomfort by keeping yourself optimistic and stopping yourself from expecting that side effects are going to happen to you" (Loftus & Fries, 2008).

Their preliminary results showed a decrease in reported side effects and a reduction in the use of medications to treat the symptoms for those who received the "special message" (Loftus & Fries, 2008). Therefore, flexibility in consent form protocols may serve as a way to maximize recovery.

To achieve a deliberate positive placebo effect during the informed consent process, we recommend three key pieces of information be included: (1) an explanation of the placebo and nocebo effect and the power of suggestion, (2) a caution against expecting symptoms solely because they were previously suggested as possible side effects of the procedure, and (3) an elucidation that positive expectancies can bring about positive results (for an example of a written paragraph to include in the informed consent, please see *Effects of the Consent Form: Using Wisdom Teeth Extractions as a Lens*). By doing so, physicians supply patients with an additional treatment tool. The tool is simply knowledge and empowerment; patients take control over their expectations, and the more optimistic expectancies may in turn influence their recovery. This method may minimize induced negative symptoms without hindering the full disclosure of potential side effects.

Empowering the individual in the recovery process is a novel way to give patients a form of control over their healing. Not only do they receive all of the

information needed to make an informed decision, they also actively partake and co-operate in all treatment routes. Enabling patient empowerment stems from much of what is discussed in this paper: a successful physician–patient interaction whereby the practitioner provides adequate information, encourages opportunities for shared decision-making, and motivates and supports the patient to participate (Trummer, Mueller, Nowak, & Stidl, 2006).

Debunking Ethical Issues

Given the role autonomy plays in contemporary bioethics and modern self-understanding, any limitations on the free choices of individuals are difficult to justify – even when they may truly improve patient recovery (Collier and Haliburton, 2011). Directly harnessing placebo effects has generally been seen as ethically problematic: deception is ubiquitous, trust is challenged, and manipulation is likely. Here, we explore how the goals of medicine influence these ethical nuances. Furthermore, and more importantly, we elucidate how using informed consent as a platform for the placebo effect limits these concerns.

The Goals of Medicine

Is the purpose of an intervention to heal or to allow individuals to achieve their own goals and desires? The tension between these two can be illustrated by a continuum: practitioner-centered care at one end and patient-centered care at the other. Practitioner-centered care, previously discussed as paternalism, aligns with the traditional biomedical model of practice, which describes the interaction of practitioners 'fixing' patients' symptoms by curing the underlying disease (Barr & Threlkeld, 2000; Stewart, 1995). Patient-centered care, by contrast, emphasizes the physical, personal and social aspects of patients' conditions (Jette, 1994), and encourages patients to take on an active role in their recovery priorities.

The two ends of this spectrum suggest different priorities for the medical system and for the individuals who use it; consequently, the way in which the

primary goal is defined has implications for what is understood to be appropriate conduct. As we will see, current practice strongly supports patient-centered care.

Deception

First and foremost, placebo conditions are believed to be inherently deceptive. By definition they are theoretically inert, yet they are often presented to the subject as an effective active treatment (O'Leary & Borkovec, 1978). Recent data indicate that "the administration of sugar pills and saline injections is in fact very low, but that clinicians commonly prescribe various active treatments with the primary intent of promoting a placebo response or complying with the wishes of the patient. The available evidence suggests that the practice of disclosure to patients regarding such placebo treatments is deceptive or at least not sufficiently transparent" (Finniss et al., 2010).

Arguments against deception are rooted in the claim that controlling patients' access to information ultimately biases their choices, thereby violating patient autonomy (Foddy, 2009). One could argue that the deception is acceptable because the end justifies the means, thus the procedure is justified because positive results can be attained. Nonetheless, the patient's autonomy is threatened by a paternalistic attitude that may influence physicians to administer placebos against the patient's knowledge or consent (Papakostas & Daras, 2001), and discourages the patient from actively participating in the recovery process.

An important consideration relates to whether and how placebo effects can be promoted without deception. Since the psychosocial context surrounding the patient (including the doctor–patient interaction and the informed consent process) can be utilized to promote a placebo effect, it is ethically sound, and clinically relevant to provide an encounter that promotes positive expectations along with honest disclosure (Finniss et al., 2010). Using placebo knowledge to elicit such a placebo effect entails no objectionable deception. In essence, the intervention – informing patients about what a placebo effect is and how this information can be implemented to enhance the recovery period – functions

based on the premise that it provides a 'fuller disclosure'. In addition to the standard account, it also relays information about how psychological factors can influence therapeutic outcome.

Abuse of Trust

A core concept of trust is "the acceptance of a vulnerable situation in which the truster believes that the trustee will act in the truster's best interests" (Thom, Hall, & Pawlson, 2004). Reminiscent again of medical paternalism, a patient might trust a physician to do what they feel is necessary to promote the greatest well being, even if that includes deception. Yet, the risk of undermining a patient's trust through deception can have arduous consequences, as it is a foundational component of the patient–physician relationship.

There is increasing evidence that patient trust, and distrust, is linked to numerous factors. First, patients adhere to treatment recommendations more often when there is a trusting relationship. Thom and colleagues (2004), for example, found that 62% of patients in the highest quartile of trust reported that they always took prescribed medication and followed their doctor's recommendation, compared with just 14% of patients in the lowest trust quartile. Second, trust is a strong predictor of continuity with providers. In the same study, the researchers found that after six months, only 3% of patients in the highest trust quartile changed physicians, compared with 24% of patients in the lowest quartile (Thom et al., 2004). Lastly, it has been suggested that trust can improve therapeutic responses by mechanisms similar to the action of placebos. In the words of Galen, one of the founders of modern medicine, "He cures most in whom most are confident" (Osler, 1905).

Researchers propose that a trusting therapeutic alliance results from the physician's attempt to respect the patient's needs and desires while following "evidence based medicine" (Barilan, 2010). Using informed consent as an intervention meets both of these requirements: it helps to initiate communication between the professional and the patient to promote respect (Brody, 1982; Faden,

Beauchamp, & King, 1986) and psychology-based empirical evidence led to its conceptualization.

Manipulation

Mental manipulation is a wide-ranging phenomenon present in almost every dimension of our social lives. Eliminating its negative connotation, it is best described as an action geared towards interfering with the decision-making process of another person, without physically limiting their options. It creates an illusion of free choice, influencing the agent to operate in a direction that under normal circumstances they would probably resist or not consider (Handelman, 2009). Consequently, it calls to question the right of the patient to determine his or her own destiny (Whan, 1983).

Although there are various types, we will concentrate on psychological manipulation. This form includes deliberate actions that influence a person by causing changes in their mental processes by any means other than reason. Flattery and guilt-induction are among some examples, yet the most relevant is subliminal suggestion (Friedman et al., 2000). Providing patients with carefully crafted suggestions fits within definitions of manipulation: "non-persuasively [and non-coercively] altering the subject's perception of … choices or understanding of the situation" (Braude & Kimmelman, 2010).

It is important to note that manipulation itself is not unethical, however certain uses can be. Where does the intervention's mental manipulation lie? The important element here is that the intervention solely provides an optional, additional treatment tool informing patients about how they can manipulate their own mental processes. It allows them to partake in their own recovery; patients are not passive participants in this environment – they may choose whether or not to modify their own expectations.

Conclusion

With ethical issues resolved, we can begin to acknowledge the extensive benefit in using the informed consent process as an autonomous, non-deceptive placebo intervention. By providing a "fuller disclosure" that includes the psychological processes involved in recovery, it has the potential to promote the therapeutic relationship, to enhance the efficacy of treatment (Keefe, Abernethy, Affleck, & Wheeler, 2008), and to offer a more comprehensive account of how to craft the process of obtaining informed consent. Using this standard-of-care tool as an intervention counteracts the potential adverse effects currently resulting from the communication process, and offers a solution to uphold and reconcile the principles of autonomy and non-malfeasance.

There is also opportunity to conduct ethical research outside of a theoretical vacuum; with a large experimental component, we can empirically study the psychological effects involved in meeting bioethical objectives. Clinical practices involving robust populations of healthy individuals with reasonable recovery times serve as a useful preliminary template. From there, we can consider implementing such a tool in innumerable areas of medicine – oncology, dentistry, psychiatry, etc. Ultimately the widespread application of an informed consent intervention may prove to be of enormous benefit to the health and welfare of a significant number of patients.

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Connecting Text 1 and 2

The process of applying theory to practice is one that is highly encouraged and deeply valued. A long-established goal in healthcare is to facilitate their integration and to continually examine, reflect and re-assess their alignment. As we have revealed in the literary review, discord occasionally occurs between ideal theory and the realities of practice. Specifically to this thesis, while ethical theory advocates for patient autonomy and non-malfeasance, informed consent practice limits their synergy. Despite the deeply rooted ethical justifications and the frequent positive consequences of informed consent, we attended to its drawback and proposed the implementation of a modified consent procedure to address this obstacle. To bridge the traditional gap between new theory and practice, this next piece empirically tests our recommended intervention. Here, we explore the informed consent process in the dental office, using wisdom teeth extractions (WTE) as a lens into the psychological underpinnings of this standard-of-care tool.

People having their third molars removed are an ideal population for research. Wisdom teeth extractions are a frequently performed surgical procedure, allowing for many potential participants. Moreover, those requiring a WTE are generally young, healthy individuals who voluntarily undergo a painful and unpleasant experience from which they will recover in 4-7 days. Thus, we were particularly interested in WTE because it is a common procedure with robust participants, and allows for quick recovery.

In the context of WTEs and placebo effects, research shows that placebo-treated patients report a substantial decrease in pain while untreated patients report a substantial increase in pain (e.g., Gracely, 1979). Other dental procedures show that placebo ultrasound (sham) treatments reduce swelling compared to the results of untreated groups (Ho et al., 1988; Hashish, Harvey & Harris, 1986). Psychological factors including suggestion and expectation therefore seem to influence the therapeutic response in this domain.

2

Effects of the Consent Form: Using Wisdom Teeth Extractions as a Lens

Erica Abbey[1]; Allan Lisbona[2]; Mel Schwartz[2]; Amir Raz[3]

[1]Department of Psychiatry, Faculty of Medicine, McGill University, Montreal, Canada

[2]Department of Dentistry, SMBD Jewish General Hospital, Montreal, Canada

[3]Departments of Psychiatry, Neurology & Neurosurgery, and Psychology, McGill University and the Jewish General Hospital, Montreal, Canada

Abstract

Informed consent is ubiquitous in modern medicine; however, the therapeutic effects it generates have been scarcely studied. In current practice, the disclosure of risks and side effects may inadvertently increase potential harm to the individual due to the power of suggestion. To counter this unwanted effect, the main objective of this study was to investigate the influence of positive suggestion during the informed consent procedure on the postoperative experience of patients undergoing wisdom teeth extractions (WTE). Using two separate consent forms, both clinically accurate but voicing orthogonal tenors, we provided a carefully formulated message about the role of expectations and nocebo effects in one compared to a standard consent form in the other. We hypothesized that the more optimistic and informative consent would decrease the expression, duration, and intensity of negative postoperative WTE symptoms (e.g., pain, trismus, swelling). Results from this randomized controlled pilot study at the Jewish General Hospital in Montreal indicated that slightly modifying consent form information and tenor decreased overall symptom severity scores on the Postoperative Symptom Severity Scale for experimental subjects compared to controls, as well as overall pain scores on the McGill Pain Questionnaire. Our findings suggest that altering expectations during the informed consent discussion may minimize manifested symptoms experienced post-surgically.

Keywords: Informed Consent, Wisdom Teeth Extractions, Placebo Effect, Symptom Severity, Pain

Introduction

Informed consent is ubiquitous in modern medicine. Once viewed simply as a legal preamble to treatment, informed consent today encompasses much more. Of utmost importance, it enables patients to make fully informed decisions about their clinical experience.

Throughout the past decade, informed consent itself has come under intense scrutiny, delving into how much information to share (e.g. Wells & Kaptchuk, 2012; Agard, 2005; Wood, Friedland, & McGrory, 2001), knowing how to foster understanding of that information (e.g. Dunn & Jeste, 2001; Joffe, Cook, Cleary, Clark, & Weeks, 2001; Kent, 1996), learning how to evaluate comprehension (e.g. Paasche-Orlow, Taylor, & Brancati, 2003; Wirshing, Wirshing, Marder, Liberman, & Mintz, 1998), and discovering how to support a voluntary decision-making process (e.g. Dermatis & Lesko, 1991; Whitney et al., 2004). Findings so far have helped to determine many of these components, such as the variables that affect understanding (e.g., time of day, language used, setting in which information is provided, state of mind of the potential participant) and decision-making (e.g., who influences the decision to consent, what matters most to the participants) (Wood et al., 2001). Scientific investigation, however, rarely focuses on the psychological underpinnings of the informed consent process; aspects which – as of yet overlooked – may carry potent therapeutic potential.

A significant part of the informed consent process includes communicating and understanding the risks involved in treatment. Disclosure of these risks fosters expectations, and these expectations can exert a towering top-down effect on behavior and circumstance (Benedetti, 2006, 2008). While most of the medical community undervalues these nuances, social psychologists have long known the extent to which expectations affect how people weigh experiences and evaluate outcomes (Kirsch, 1985; Raz, 2007a, 2007b). They can also trigger internal healing responses, otherwise known as a placebo effect (Benedetti, 2010). The placebo effect is a phenomenon wherein patients' positive

expectations lead to health benefits. Its converse, deemed the nocebo effect, denotes the worsening of symptoms due to negative expectations (Colloca & Miller, 2011).

With the knowledge that the words of the informed consent encounter can inadvertently produce nocebo effects (Wells & Kaptchuk, 2012), it follows that the obligation to obtain informed consent potentially contends with the physician's obligation to do no harm. Accordingly, physicians must face the ethical challenge of communicating risks to patients without undermining autonomy or non-malfeasance (Colloca & Miller, 2011; Wells & Kaptchuk, 2012). To address this dilemma, the present study proposes a solution that not only minimizes nocebo responses, but also elicits a placebo effect to enhance patient recovery.

Literature indicates that just as expecting symptoms can lead to their manifestation, understanding placebo and nocebo effects and the power of expectations can defend against those negative consequences (Loftus & Fries, 1979). For instance, in an unpublished pilot study with scleroderma patients at the Stanford University Medical School, Loftus and Fries (2008) incorporated a special message into the informed consent discussion explaining the powerful role expectations play in producing unlikely symptoms. In testing the efficacy of a particular drug cocktail (propanolol and alpha-methyldopa), patients received either a standard informed consent message or one that incorporated the "special message." Both forms included possible side effects, including known ones and some implausible made-up ones that had not been associated with the drug (e.g., ringing in ears, burning sensation in feet). Their pilot study revealed that all participants, regardless if given drug or placebo, experienced the physiologically likely and unlikely symptoms. Interestingly, their preliminary results showed a decrease in reported side effects and a reduction in the use of medications to treat the symptoms for those who received the "special message" (Loftus & Fries, 2008).

Our study aimed to build upon previous research by Loftus and Fries, and to generate a comprehensive account of the impact consent forms may have on therapeutic outcome. We implemented and tested a psychological intervention that stimulated a placebo effect during the informed consent discussion preceding wisdom teeth, or third molar, extractions. Alongside the standard consent form, we provided a carefully formulated message about the power of expectations in garnering different postoperative outcomes. In our experimental group, we emphasized caution against expecting symptoms solely because they were previously suggested and encouraged patients to take control of their recovery. We hypothesized that this approach would, in turn, decrease the expression and/or duration of negative postoperative symptoms.

Methods*

Participants

Dental secretaries in the Department of Dentistry at the Sir Mortimer B Davis Jewish General Hospital (SMBD-JGH) recruited 48 participants (21 males, 27 females) who would be undergoing a WTE procedure. The participants spoke and understood either English or French, or both. We excluded those who smoked (n=5), possessed a diagnosis of a severe medical or mental illness (n=1), only had upper third molars extracted (n=6), or did not fully complete the three postoperative assessments (n=4). These exclusion criteria were decided upon for the following reasons: research shows that smoking increases the risk and severity of many post-operative symptoms, such as alveolar osteitis (dry socket) and pericoronitis (Berge & Boe, 1994; Ferrus-Torres et al., 2011; Grossi et al., 2007); those who possess a severe medical or mental illness may either have a sickness that directly interferes with the healing process or are on medication that may do so; (3) to help control for differences in symptom severity between participants with varying numbers of teeth removed, a committee comprised of

* The Ethics Committee at the SMBD-JGH in Montreal approved the study protocol.

oral surgeons and dental researchers advised that at least one lower third molar must be extracted; and (4) incomplete assessments resulted in missing data, which were therefore discarded.

After adjusting for the exclusion criteria, 32 out of the 48 participants recruited were included in this study (16 control [8 men, 8 women], 16 experimental [8 men, 8 women]). Gender was evenly split between the two groups by random occurrence. A priori sample size calculations with alpha level = 0.05, anticipated effect size = 0.80, and desired statistical power level of 0.70 concluded that the minimum total sample size requirement was 32 participants (Soper, 2006). Participation was voluntary and no compensation was given.

Materials and Procedure

On the day of the WTE procedure, patients gave written consent to participate in the study and filled out a questionnaire (see Appendix A) relating to their health status and current concerns towards WTE postoperative complications. The participants were randomized, by flip of a coin, into the control or experimental conditions. They remained unaware of the group to which they belonged.

Using an mp3 player, participants in the control group listened to the following innocuous 1 m 11 s tape recording:

> *You are about to undergo a wisdom tooth extraction. This is a surgical procedure to remove one or more wisdom teeth. Wisdom teeth are the four permanent adult teeth located at the back corners of your mouth. They begin to emerge from your gums between the ages of 17 and 24. Nowadays people often have jaws that are too small for all 32 teeth. As a result, there may not be enough space for wisdom teeth to come through properly. In some cases, the wisdom teeth may become impacted and are therefore unable to break through the gums. In other cases the wisdom teeth may come in at awkward angles. When wisdom teeth are not removed, it is*

possible that other teeth will shift due to the lack of space. Your wisdom teeth extraction will correct an actual problem or will prevent problems that may come up in the future.

Members of experimental group listened to a different message of the exact same length. This additional text constituted the independent variable of the study. It read as follows:

You should keep in mind this important point about side effects. Research has shown that simply mentioning possible annoying symptoms causes some people to actually experience them. This happens because of a person's expectations. When side effects are mentioned, some people automatically expect that they will occur. This expectation can then lead to the actual experience of the side effects. As you can see, expectations of an outcome have the ability to influence the outcome itself. Fortunately, you can guard yourself against these sorts of discomfort. You can do this by keeping yourself optimistic about your recovery period and stopping yourself from expecting that side effects are going to happen to you. You may be able to reduce the manifestation and/or duration of symptoms. Believing that these symptoms will not occur may have the power to decrease their occurrence. It is therefore helpful to be mindful of this phenomenon and remain positive about your experience.

No alterations were made to the actual dental procedure. After the WTE, the oral surgeon, or a member of his staff, filled out a modified version of Pederson's difficulty index scale for removal of impacted third molars to indicate the complexity and difficulty of the surgical procedure (Yuasa, Kawai, & Sugiura, 2002) (see Appendix B).

Participants completed post-operative online assessments (see Appendix C) at intervals of 24, 48, and 72 hours following the extraction. A research member

contacted the participants by phone at each time point to remind them to complete the daily assessment. At the first assessment time point, participants were sent a standardized email that provided them with the website URL (a LimeSurvey® web-based application tool) and outlined the instructions for questionnaire completion. Participants were instructed to fill out the questionnaire just prior to taking the next dose of analgesics within a set time range.

Main Outcome Measures

The postoperative online assessment constituted the dependent variable of this study. To measure pain levels, we asked subjects to answer the Numerical Rating Scale for Pain (NRS-11) (Downie et al., 1978), where patients rated their pain on a scale from 0 to 10 (0 = no pain and 10 = the worst possible pain imaginable), and the McGill Pain Questionnaire (MPQ) (Melzack, 1975), where patients assessed what their pain felt like and how strong it was. A modified Postoperative Symptom Severity Scale (PoSSe) (Ruta, Bissias, Ogston, & Ogden, 2000) was administered to assess seven subscales: eating (enjoyment of food and ability to open mouth), speech (speech and voice), sensation (tingling and numbness), appearance (bruising and swelling), pain (duration and painkiller effectiveness), sickness (presence and frequency of nausea), and interference with activities (daily, leisure, and pain affecting life). We also asked patients to record analgesics prescribed and the dosage taken. We hypothesized that experimental subjects would indicate lower pain and symptom severity ratings compared to control subjects on all outcome measures and would have a reduced analgesic intake.

Statistical Analysis

All data were analyzed using SAS, version 9.2. Independent t-tests evaluated group differences for age, number of teeth extracted, difficulty of extraction, duration of the surgical procedure, and preoperative concerns regarding postoperative WTE complications. To determine if there were significant differences in recovery between conditions, differences in assessment scores were examined with 2x3 repeated-measures analyses of variance (ANOVAs) using condition (control, experimental) as the between-subjects factor and time (24 hours, 48 hours & 72 hours post WTE) as the within-subjects factor in each outcome measure model. Repeated-measures ANOVAs were also run for the seven PoSSe subscales.

Results

The independent t-tests indicated no significant differences between the two groups (control and intervention) with respect to age, number of teeth removed, difficulty of the extraction, duration of the surgical procedure, or preoperative expectations **(**see Table 1**)**.

Table 1. Means, standard deviations, and levels of significance for potentially confounding variables

	Mean (SD)		P-value
	C (*N=16*)	E *(N=16)*	
Age	22.25 (2.72)	21.50 (3.44)	0.25
Number of teeth removed	3.44 (0.96)	3.63 (0.89)	0.71
Degree of difficulty	5.03 (1.46)	5.16 (1.70)	0.59
Duration	44.06 (10.68)	46.25 (9.04)	0.73
Preoperative expectations	38.75 (8.00)	39.06 (12.00)	0.53

Note. C = control condition. E = experimental condition. Standard deviations are in parentheses. No significant differences were found between control and experimental conditions for number of teeth removed, number of teeth removed, degree of difficulty, duration of extraction, or preoperative concerns.

Table 2 presents descriptive statistics and levels of significance for the PoSSe, the MPQ, and the NRS-11.

Table 2. Means, standard deviations, and levels of significance for the PoSSe, MPQ, and NRS-11

Outcome Variable	Mean (SD)						Overall Main Effect of Condition	
	24 hr		48 hr		72 hr			
	C	E	C	E	C	E	F	p-value
PoSSe	39.9 (3.9)	31.8 (2.7)	31.7 (4.0)	22.2 (1.9)	26.8 (3.8)	19.3 (2.5)	11.02	0.002**
Eating								
Enjoyment	8.2 (3.3)	7.5 (2.7)	7.5 (3.3)	6.9 (2.5)	6.5 (4.0)	4.9 (3.6)	2.16	0.152
Trismus	5.7 (4.1)	3.1 (3.2)	5.3 (4.7)	1.5 (1.7)	3.4 (2.5)	1.6 (2.5)	13.92	0.001***
Speech								
Voice	0.6 (1.2)	0.5 (1.0)	0.4 (0.9)	0.3 (0.7)	0.0 (0.0)	0.2 (0.9)	0.00	1.000
Speech	1.8 (1.4)	1.0 (0.8)	0.7 (1.0)	0.7 (0.6)	0.4 (0.8)	0.4 (0.8)	1.84	0.185
Sensation								
Tingling	2.5 (2.0)	2.4 (1.8)	0.6 (2.0)	0.5 (1.2)	0.1 (0.5)	0.1 (0.5)	0.08	0.786
Numbness	3.4 (1.7)	3.5 (1.2)	1.1 (2.7)	0.6 (1.2)	0.3 (0.7)	0.3 (0.7)	0.16	0.694
Appearance								
Bruising	0.1 (0.4)	0.4 (0.7)	0.5 (1.5)	0.3 (0.6)	0.8 (1.6)	0.5 (0.9)	0.08	0.775
Swelling	3.3 (2.9)	2.7 (2.6)	3.0 (2.9)	3.2 (2.4)	2.6 (2.5)	3.1 (2.1)	0.01	0.938
Pain								
Duration	5.3 (3.2)	2.8 (2.5)	5.2 (3.8)	2.3 (1.5)	4.9 (3.5)	2.0 (1.7)	22.64	0.000***
Painkillers	3.7 (1.2)	3.0 (1.4)	4.0 (2.1)	2.8 (2.0)	4.2 (2.2)	3.1 (2.2)	6.44	0.017*
Sickness								
Nausea	0.5 (0.8)	0.9 (1.4)	0.2 (0.7)	0.2 (0.5)	0.4 (1.0)	0.3 (0.9)	0.29	0.593
Frequency	0.6 (1.1)	0.8 (1.3)	0.2 (0.5)	0.2 (0.5)	0.3 (0.7)	0.2 (0.4)	0.00	1.000
Interference								
Daily	1.4 (1.3)	1.3 (1.4)	0.8 (1.3)	1.0 (1.3)	0.8 (1.3)	0.9 (1.2)	0.11	0.746
Leisure	1.5 (1.1)	1.2 (0.9)	1.1 (0.9)	1.0 (0.8)	1.0 (1.1)	1.1 (0.9)	0.27	0.605
Life	1.1 (0.8)	0.6 (0.7)	1.0 (1.0)	0.6 (0.7)	1.2 (1.0)	0.6 (0.8)	8.04	0.008**
MPQ	37.8 (4.1)	32.4 (3.2)	37.9 (3.8)	27.6 (3.0)	35.1 (3.8)	26.0 (3.4)	8.03	0.008**
Current Pain	1.4 (0.6)	1.2 (0.4)	1.6 (0.8)	1.3 (0.5)	1.6 (0.9)	1.3 (0.4)	5.81	0.040*
NRS-11	2.3 (0.5)	2.1 (0.3)	2.3 (0.5)	2.0 (0.2)	2.1 (0.6)	1.5 (0.3)	1.22	0.278

Note: N=32 (16 C, 16 E). C = control group; E = experimental group. Standard deviations are in parentheses. Means and standard deviations are recorded per assessment time point (24, 48, 72 hrs post-extraction).
The repeated-measures ANOVA indicated that experimental participants reported significantly lower PoSSe and MPQ scores. The experimental condition also had lower scores on the trismus, pain duration, painkiller effectiveness, and pain affecting life questions.
df = (1,30)
* $P \leq 0.05$
** $P \leq 0.01$
*** $P \leq 0.001$

Postoperative Symptom Severity Scale

Overall, participants in the experimental condition produced significantly lower mean PoSSe scores compared to those in the control group (see Figure 1), with a two-way repeated measures ANOVA demonstrating a significant main effect for condition ($F(1,30) = 11.02$, $p < 0.01$). Differences of least square means revealed significance only 48 hours post-extraction ($F(2,60) = 9.46$, $p < 0.05$).

Figure 1. Mean scores for control and experimental participants on the Postoperative Symptom Severity Scale per assessment time point

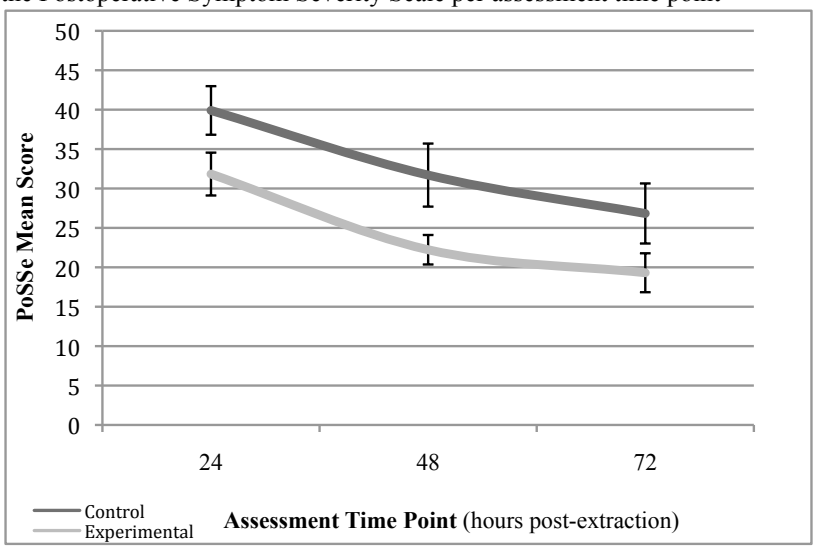

Figure 1. Experimental participants reported significantly lower scores on the PoSSe compared to controls 48 hours post-WTE ($p<0.05$), indicating that patients in the experimental group experienced less severe symptoms. Standard errors are presented in the figure by the error bars attached to each column. N=32 (16 control; 16 experimental)

Pain: The 'pain' subscale on the PoSSe was composed of two questions: 'Thinking of the past day, how many hours did you experience pain from your operation?' and 'Thinking of the past day, has the pain from your operation been controlled by painkillers?' The results from the ANOVA showed significant overall main effects of condition for both questions ($F(1,30) = 22.64$, $p < 0.001$ and $F(1,30) = 6.44$, $p < 0.05$). The control condition experienced more hours of pain compared to the intervention group (see figure 2a), and the intervention group experienced better painkiller relief compared to controls. Differences of least square means revealed significant condition differences for the first pain question at all time points (24 hours: $F(2,60) = 2.52$ $p < 0.01$; 48 hours: $F(2, 60) = 2.87$ $p < 0.01$; 72 hours: $F(2, 60) = 2.88$ $p = 0.01$).

Interference with activities: The 'interference with activities' subscale honed in on the degree to which pain affected participants' lives. We found a significant overall main effect for condition ($F(1,30)=8.04$, $p<0.01$), wherein the intervention group's lives were less affected by the pain from their operation compared to the control group (see figure 2b).

Eating: One of the two questions in the 'eating' subscale was used as a proxy for trismus, a common WTE symptom marked by being unable to normally open the mouth. The repeated measures ANOVA indicated a significant overall main effect for condition ($F(1,30) = 13.92$, $p < 0.001$), where the manifestation and severity of trismus was less for the experimental condition compared to controls. Differences of least squared means revealed significance 24 hours ($F(2, 60) = 2.63$, $p < 0.05$) and 48 hours ($F = 3.77$, $p < 0.01$) post-extraction (see figure 2c).

Speech: Within the subscale 'speech', when rating how badly patients' voice was affected, the control condition showed significantly higher scores 24 hours post-extraction ($F(2,60)=0.78$, $p<0.05$) compared to the intervention group.

The 'sensation', 'appearance', and 'sickness' subscales showed no significant differences between conditions.

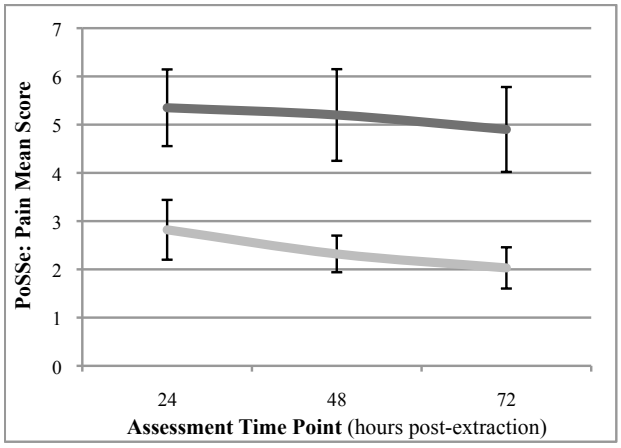

Figure 2a. Mean pain scores for control and experimental participants on the Postoperative Symptom Severity Scale per assessment time point

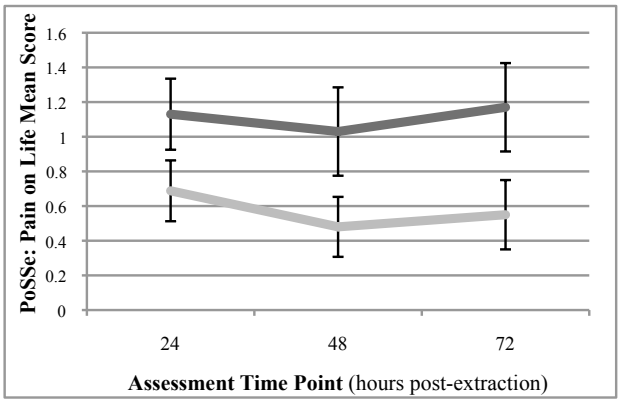

Figure 2b. Mean pain affecting life scores for control and experimental participants on the Postoperative Symptom Severity Scale per assessment time point

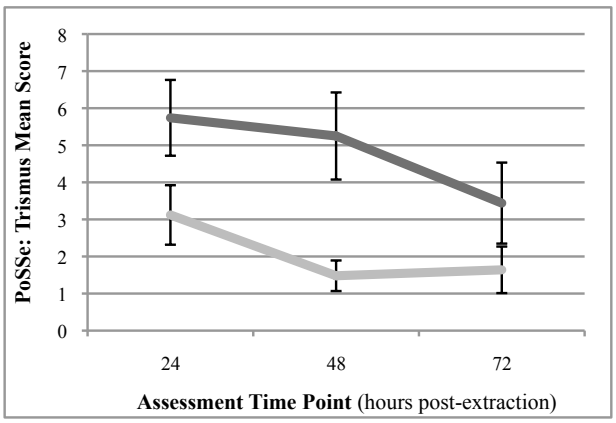

Figure 2c. Mean trismus scores for control and experimental participants on the Postoperative Symptom Severity Scale per assessment time point

Figures 2a-2c. 2a: Experimental participants experienced significantly less pain compared to controls 24, 48, and 72 hours post-WTE ($p<0.01$). *2b:* Pain experienced by experimental patients affected their lives significantly less than controls ($p<0.01$); *2c:* Experimental participants reported significantly less trismus compared to controls 24 and 48 hours post-WTE ($p<0.05$). Standard errors are presented in the figure by the error bars attached to each column. N=32 (16 control; 16 experimental).

McGill Pain Questionnaire

Pain, as assessed by the McGill Pain Questionnaire (MPQ), was found to be significantly lower ($F(1,30) = 8.03$, $p < 0.01$) in the intervention group **(**see Figure 3**)** compared to controls. Differences of least square means revealed significance only 48 hours post-extraction ($F(2,60) = 10.31$, $p < 0.05$).

Figure 3. Mean scores for control and experimental participants on the McGill Pain Questionnaire

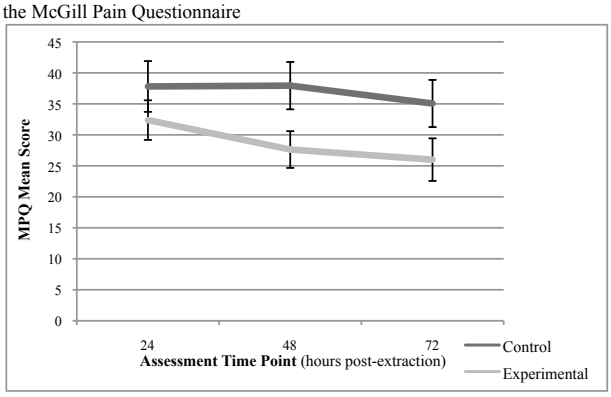

Figure 3. Mean pain scores for control and experimental groups on each assessment day. Experimental participants reported significantly less pain compared to controls 48 hours post-WTE ($p<0.05$). Standard errors are presented in the figure by the error bars attached to each column. N=32 (16 control; 16 experimental).

Looking at the specific question on the MPQ, "Which word describes your pain right now?" a significant difference was found between the control and experimental groups ($F(1,30) = 5.81$, $p < 0.05$), with the control group reporting worse pain compared to the experimental group (see Figure 4).

Figure 4. Overall Description of Current Pain on the McGill Pain Questionnaire

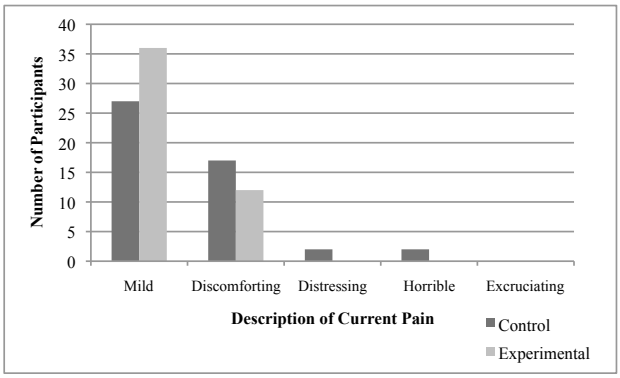

Figure 4. An overall description of current pain for control and experimental groups over the three time points. Patients in the experimental group only indicated mild and discomforting pain while control patients ranged from mild to horrible. The experimental group reported the lowest category of pain more often than controls. N=32 (16 control; 16 experimental).

Numeric Rating Scale for Pain

The repeated-measures ANOVA demonstrated no significant differences in patient pain scores between control and intervention group for the Numerical Rating Scale.

Medication

All patients were prescribed over-the-counter analgesics. The oral surgeon prescribed ibuprofen to all of them. Thirty-one participants additionally managed their pain with percocets, while the remaining patient (experimental) used codeine. The surgeon also prescribed antibiotics. Twenty-nine participants (15 control, 14 experimental) received teva-amoxicillin; two (1 control, 1 experimental) received ratio-clarithromycin; and one patient (experimental) received clindamycin.

Medication use was compared between control and experimental groups. Participants indicated if they were taking medication as prescribed, less than prescribed, or more than prescribed. The repeated measures ANOVA revealed an overall main effect for condition ($F(1,30)=9.30$, $p<0.01$), indicating that the experimental group consumed fewer analgesics compared to controls (refer to Table 3 for the frequency distributions of analgesic consumption).

Table 3. Frequency Distribution of Overall Analgesic Consumption

	Control	Experimental
Less than prescribed	12.5%	35.4%
As prescribed	81.25%	64.6%
More than prescribed	6.25%	0%

Note: N=32 (16 control; 16 experimental).

Discussion

The present study demonstrated that the informed consent process can dually serve as an ethical requisite as well as an autonomous intervention. Following third molar extractions, participants who received a special message about the role expectations play in recovery experienced significantly less overall symptom severity compared to controls, as measured by the PoSSe and the MPQ. These results indicate that modifying the informed consent process – by explaining placebo/nocebo effects and suggesting that patients can control their therapeutic outcome – lessens the severity of the recovery period.

Contemporary views hold that health involves more than the absence of disease, and this perspective underscores the importance of quality of life issues (Slade, Foy, Shugars, Phillips, & White, 2004). The physical, psychological, and aesthetic ramifications associated with third molar extraction side effects can significantly impact postoperative quality of life (see review by Slade et al., 2004). The intervention employed in the current study addressed this link directly, with patients in the intervention group reporting that pain affected their lives considerably less compared to the control group.

The difference in analgesic consumption between the control and experimental conditions also constituted a central finding in this study. Almost 3-times as many participants in the intervention group reported using fewer analgesics than were prescribed compared to controls. Furthermore, no participants in the experimental group indicated taking more medication than they were prescribed. The intervention patients also indicated that the painkillers were significantly more effective in controlling their pain. These findings have major implications, as consumption of pain medication is accompanied by unwanted side effects and adverse complications (Raz, 2005). Accordingly, using the power of suggestion as an alternative treatment to medication could improve patients' overall health outcomes.

Our findings indicated that control and experimental participants did not significantly differ on the PoSSe 'sensation' and 'appearance' subscales. These results led to two potential conclusions: either the tailored message given to experimental subjects did not sufficiently target the particular side effects, or the power of suggestion and expectation did not influence these symptoms. The latter aligns with prior research: whereas pain is a psychological function with physiological substrates, complications such as swelling and bruising are physiological functions that are not subject to psychological states. Unlike placebo effects on pain, data have yet to establish expectation induced placebo effects on physiological functions that are unmediated by psychological processes (Harrington, 1999). Indeed, a recent study by Benedetti (2003) revealed that conditioning plays a crucial role in the placebo responses of unconscious physiological functions, whereas expectations replace conditioning when conscious perception is involved (e.g., pain) (Benedetti et al., 2003) (Please see *Informed Consent as a Therapeutic Intervention: Reconciling Autonomy and Non-Malfeasance through a Place Effect* for more information about conditioning and expectancy theories). Compatible with the proposed theory, our intervention, which used expectation as a vehicle to elicit a placebo effect, primarily targeted pain reduction.

'Feelings of sickness' was the only other subscale to show non-significant findings. Sickness after WTE surgery is usually attributed to anesthetic use and medication prescribed post-operatively. Participants in this study underwent similar anesthetic procedures and were prescribed comparable analgesics and antibiotics, which justified the non-significant findings.

The presence of a placebo effect at certain assessment time points and not others was an unexpected finding. The voice question on the PoSSe, and the overall PoSSe and MPQ showed significant differences only 24 and 48 hours post-extraction, respectively. Because of the novelty of this study, directly related empirically tested research inadequately explains these results, and further investigation would be required to probe these nuances. Nonetheless, we

propose a potential explanation based on related theory. To explain the overall PoSSe and MPQ findings, we referred to a meta-analysis by Kirsch et al. (2008) investigating the efficacy of antidepressants compared to placebos. The researchers found that efficacy depended on initial severity, wherein only trials involving the most extremely depressed patients reached clinical significance, and it was determined to be due to a decrease in the response to placebo rather than an increase in the response to medication (Kirsch et al., 2008). We can relate these findings to the present study, and propose that symptoms 24 hours post-extraction were too severe and were therefore above the threshold of placebo effectiveness. It is possible that it was only once the symptom severity decreased by the second assessment time point (48 hours post-WTE) that the placebo effect was able to occur.

With regards to the finding about WTE affecting voice, symptom severity ratings were very mild at the first assessment time point and trended towards being an absent symptom by the second and third. The difference between experimental and controls, therefore, only presented itself when there was substantive manifestation of the symptom.

There were certain limitations to our study. First, the sample size (n=32) was small, which reduced the likelihood of achieving statistical significance. It would be interesting to see if a larger cohort would ascertain more significance between the control and experimental conditions. In addition, research indicates that the variables affecting postoperative recovery are: gender, race, age, smoking habits, alcohol consumption, length of procedure, number and location of teeth extracted, and degree of difficulty of the extraction (Capuzzi et al., 1994). While we excluded smokers and patients with only upper extractions, and implemented a randomized controlled trial design to control for the other potential confounds, we acknowledge that our small sample size might have prevented us from adequately doing so.

The questionnaires we used in this study are widely accepted measurement systems for assessing postoperative pain after third molar removal. They provide

accurate quantifiable data on the patients' experience of symptoms (see Kanatas & Rogers, 2010; Ruta et al., 2000; Seymour, Meechan, & Blair, 1985; Wirth, Brenlan, Levine, & Rodriguez, 1993) and evaluate many of the known side effects. In interpreting the comprehensive data, several statistical analyses were computed per questionnaire without adjusting for multiple comparisons, which was therefore a limitation of this study. Additionally, instruments of this type have obvious experimental limitations since they are susceptible to bias due to their highly subjective nature. While the subjective data provided information on the patients' experience of pain, our data set would have benefitted from objective measurements for the symptoms assessed in the PoSSe, such as measuring aperture of mouth, diameter of bruises, and tactile sensitivity. It would have also been advantageous to compare participant scores with scores from a witness of the recovery period for measures such as interruption in daily and leisure activities.

Subjective bias may help explain the non-significant findings on the Numerical Rating Scale-11 (NRS-11). Patients consider many variables (e.g. distress, tiredness, mobility, impact on activity, and/or global satisfaction) when evaluating their subjective experience, and may incorporate these extraneous factors specifically when using numeric rating scales (Williams, Davies, & Chadury, 2000). To avoid this bias, the majority of WTE studies investigating pain as the outcome variable tend to use the more resilient Visual Analog Scale (VAS) (e.g. Price, McGrath, Rafii, & Buckingham, 1983; Vallerand, Vallerand, & Heft, 1994). We administered the NRS-11 rather than the VAS because the VAS was incompatible with our methods of web-based data collection. Importantly, despite the assumed advantages of the VAS, studies demonstrate NRS-11 measures as equivalent to VAS scores (e.g. Breivik, Bjornsson, & Skovlund, 2000; Hartrick, Kovan, & Shapiro, 2003).

Two other types of bias may have affected our findings. Although the participants were blind to the group to which they belonged, the researcher was not, which increased the chances of an experimenter-expectancy bias.

Experimenter-expectancy bias occurs when the researcher's expectancies affect research results, usually by unconsciously influencing the participants (Hazelrigg, Cooper, & Strathman, 1991). A WTE study investigating placebo analgesia revealed such an effect. Patients undergoing WTE assessed their pain using the McGill Pain Questionnaire before and after an intravenous injection. The patients were told that they might receive an opioid analgesic (fentanyl), an opioid antagonist (naloxone), or placebo (saline), and that these medications might decrease, increase, or have no effect on their pain. Only the clinician administering the drugs knew that one group would receive placebo or naloxone, but not fentanyl, and that the other group would receive placebo, naloxone, or fentanyl. Pain after placebo administration in the latter group was significantly less than pain in the former. This result indicated that the clinician's knowledge may result in subtle behaviours that influence patient responsiveness (Gracely, Dubner, Deeter, & Wolskee, 1985).

The other effect we may have encountered was the response bias, wherein participants respond to questions in a way that would please the researcher (Hrobjartsson et al., 2011). It is difficult to distinguish between a true placebo effect and response bias on subjective outcomes. As previously stated, it would be beneficial for future research to record and analyse objective measurements (Hrobjartsson & Gotzsche, 2001).

Conclusion

The findings from this study suggest that both the content of information provided to a patient and the informed consent process itself need further consideration. Our results support and reinforce the notions put forth by Loftus and Fries (2008): first, patients should receive a clear, direct, and accurate statement about the procedure followed by its general level of risk. Second, all information, general or specific, should be available to individuals at all times. Finally, when discussing information about specific risks and symptoms during

the informed consent procedure, clinicians should present information to patients in the context of nocebo effects, including, but not limited to, why they occur and how to guard against them (Fries & Loftus, 1979). This discussion should therefore incorporate an explanation of how a person's expectations may actually cause negative experiences, and how taking control of, managing, and manipulating one's expectations can reverse these effects. Our data suggest that this tactic may minimize induced symptoms.

The informed consent process is more than a legal necessity or a requisite for patient autonomy. It is a method of shaping expectations and guiding psychological and physiological processes, which has clear implications for healing. Consequently, we must acknowledge the possibility of iatrogenic harm as a direct result of this modern day ritual and consider how its effects can be minimized, or even reversed. Our findings provide new insight into this seemingly neutral process, and suggest that we should craft informed consent as an encounter that gives maximum therapeutic value to patients. Educating those who create consent forms and those who deliver the information, such as hospital Ethics Committees and clinicians, is paramount. Fundamentally, continuing this research trajectory will likely pave the way to a more scientific and effective way of constructing consent forms to the patient's advantage.

Acknowledgements

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Connecting Text 2 and 3

Effects of the Consent Form: Using Wisdom Teeth Extractions as a Lens demonstrated that modifying the informed consent to accommodate psychological processes enhanced recovery. While we used third molar extractions as a proxy to study these particular psychological effects, it was important for us to also consider and control for the other factors that determine therapeutic outcome. Several studies have identified a plethora of variables associated with post-extraction pain, such as demographic, anatomic, and operative features, yet very few analyses have included psychological factors in their framework. By using data from our previous body of work, the next piece addresses this oversight, and explores the determinants of post-extraction pain when taking patients' preoperative expectations into account. Furthermore, we ascertain whether receiving the modified consent is an accurate predictor in reducing post-surgical pain.

3

Expectation as a Determinant of Pain Following Removal of Third Molars

Erica Abbey[1]; Allan Lisbona[2]; Mel Schwartz[2]; Amir Raz[3]

[1]Department of Psychiatry, Faculty of Medicine, McGill University, Montreal, Canada

[2]Department of Dentistry, SMBD Jewish General Hospital, Montreal, Canada

[3]Departments of Psychiatry, Neurology & Neurosurgery, and Psychology, McGill University and the Jewish General Hospital, Montreal, Canada

Abstract

Context: Factors thought to influence the incidence and magnitude of pain following removal of third molars include age, gender, smoking, number of teeth removed, difficulty of extraction, surgeon experience, anesthetic technique, and operation time. Seldom considered are patients' preoperative expectations of post-extraction pain.

Objectives: The objective was to identify the determinants of pain after third molar extractions when taking psychological variables into account.

Study Design: This cohort study consisted of patients who had one or more third molars removed between 2010 and 2011 at the SMBD Jewish General Hospital in Montreal. Risk factors were grouped into psychological, demographic, anatomic, and operative categories. The outcome variable was pain, as assessed by the Postoperative Symptom Severity Scale. Data were analyzed using descriptive and multivariate statistics.

Results: The study sample was composed of 38 patients (55.26% male; age range 18-28). Preoperative expectation was the largest predictor of postoperative scores. The presence of an informed consent intervention, aimed at managing expectations, was associated with a decreased risk of post-extraction pain. No demographic, anatomic, or operative factors were significant determinants when controlling for expectations.

Conclusion: Our findings show that psychological factors help to explain 43% to 55% of the variance of pain reported after the removal of third molars. This study reveals that expectations are a highly important consideration in determining therapeutic outcome.

Keywords: Third Molar Extraction, Risk Factors, Determinants of Pain, Expectations

Introduction

The surgical removal of wisdom teeth, also known as third molars, is one of the most commonly performed operations by oral and maxillofacial surgeons (Mercier & Precious, 1992). It is a procedure often associated with postoperative complications; most notably, patients experience pain for several days (Bouloux, Steed, & Perciaccante, 2007; Ferrus-Torres et al., 2011; Lago-Mendez et al., 2007). Pain in the oro-facial area of the human body has physical and psychological ramifications that can have a significant impact on patients' quality of life (Al-Khateeb & Nusair, 2008).

Factors presumed to influence the incidence and magnitude of pain following third molar removal generally include age, gender, smoking, number of teeth extracted, difficulty of the procedure, surgeon experience, anesthetic technique, and operation time (Bouloux et al., 2007; Bui et al., 2003; Mobilio et al., 2011; Oikarinen, 1991). Conclusions drawn from individual studies, however, are often inconsistent and divergent from one another (see Table 1). The variability in findings may be due to disparate definitions of complications, study design, different methods of evaluating study variables, selection bias, misclassication bias, or poorly controlled confounding variables (Bouloux et al., 2007; Bui et al., 2003).

An alternate explanation for the variability in findings is a factor seldom considered: the patient's expectations. Expectation is a powerful modulator in everyday life (Tracey, 2010) and it can lead people to experience feelings and symptoms that they would not otherwise feel (e.g. Barsky et al., 2002; Beecher, 1955; Flaten, 1998; Hahn, 1997; Shapiro & Morris, 1978). Literature has shown that patients' positive expectations are likely to improve outcome, whereas negative expectancies are likely to make it worse (Benedetti et al., 2007). These phenomena are known as the placebo and nocebo effect, respectively.

Table 1. Conclusions from a sample of peer-reviewed articles on the determinants of post-third molar extraction pain

	Significant determinant of pain	**Non-significant determinant of pain**
Age	Grossi et al. (2007); Bui, Seldin, & Dodson (2003); Phillips, White, Shugars, & Zhou (2003); Capuzzi, Montebugnoli, & Vaccaro (1994)	Conrad et al. (1999); Fischer, Frame, Rout, & McEntegart (1988)
Gender	Sato, Asprino, de Araujo, & de Moraes (2009); Benediktsdottir, Wenzel, Petersen, & Hintze (2004); Phillips, White, Shugars, & Zhou (2003); Conrad et al. (1999); Fischer et al. (1988)	Ip, Abrishami, Peng, Wong, & Chung (2009); Grossi et al. (2007); Van Wijk & Kolk (1997)
Smoking	Larsen (1992)	Capuzzi et al. (1994)
Number teeth removed	Susarla & Dodson (2004)	Bui et al. (2003)
Difficulty of extraction	De Boer, Raghoebar, Segenga, Schien, & Boering (1995); Clauser & Barone (1994); Berge & Gilhuus-Moe (1993); Oikarinen (1991)	Meechan & Seymour (1993); Parsloe, Chater, Bembridge, & Simpson (1988); Seymour, Blair, & Wyatt (1983)
Surgeon expertise	Phillips, White, Shugars, & Zhou (2003); Capuzzi et al. (1994); Berge & Gilhuus-Moe (1993); Sisk et al. (1986);	Grossi et al. (2007); Benediktsdottir et al. (2004); Rehman, Webster, & Dover (2002); De Boer et al. (1995)
Anesthetic technique	Edwards, Brickley, Edwards, Shepherd, & Horton (1998); Holland & Stassen (1996)	Bui et al. (2003)
Operation time	Lago-Mendez et al. (2007) Conrad et al. (1999); Pedersen (1985)	Grossi et al. (2007) Benediktsdottir et al. (2004); Monaco, Staffolani, Gatto, & Checchi (1999); Berge & Gilhuus-Moe (1993)

Prior to third molar extractions, patients generally form negative impressions of the recovery period. Individuals develop these expectations from several sources, such as past dental experiences, specifically a past tooth extraction, or from friends' anecdotal stories of the procedure. Consent forms for surgery – which include a list of side effects – may further cultivate patients' pessimistic outlooks (Wells & Kaptchuk, 2012). These negative expectancies may actually increase the likelihood and severity of postoperative pain through the nocebo effect.

Objectives and Hypotheses

The objective of this study was to identify the risk factors associated with post-extraction pain. In particular, we investigated the influence of expectations on the manifestation of pain following third molar surgery while controlling for demographic, anatomic, and operative variables. We hypothesized that preoperative expectations would be a leading determinant.

The current study was derived from a larger paradigm exploring the effects of actually modifying patient expectancies prior to wisdom teeth extraction surgery. We tested the efficacy of a psychological intervention implemented during the informed consent process that provided patients with information about how and why they should manipulate their expectancies. The sample was randomized into control and experimental groups, where the former underwent the standard consent procedure with an additional innocuous message, and the latter received the standard consent along with a message about the role expectations play in the recovery process. To account for this variation, intervention status (either present or absent) was included in the present study as a control variable. We hypothesized that subjects who received the intervention would have a less severe recovery period compared to those who were in the non-intervention group.

Due to such variability in findings from previous reports, we retested age, gender, number of third molars removed, difficulty of extraction, and operation time as risk factors. We hypothesized that at least one demographic, anatomic, or operative variable would help contribute to the explanation of postoperative pain when controlling for patients' preoperative expectations.

Methods

The Ethics Committee at the Sir Mortimer B Davis Jewish General Hospital (SMBD-JGH) in Montreal approved the study protocol.

Patients

Patients scheduled for third molar surgery with one oral surgeon at the SMBD-JGH Department of Dentistry were considered eligible for this study. Patients were excluded if they met any of the following criteria: (1) younger than 18 or older than 28 years of age; (2) diagnosed with a severe medical or mental illness; (3) or smoked cigarettes.

Between August 2010 and December 2011, 48 patients (21 males, 27 females) were recruited to participate. Five patients were smokers, one patient had a mental illness diagnosis, and four patients did not complete the postoperative assessments. These patients were therefore excluded. Thus, 38 patients (21 males and 17 females) participated in this study.

The dental secretary recruited participants by phone before their extraction appointment. On the day of surgery, prior to the third molar extraction, patients were verbally and in writing informed about the details of the study and thereafter signed a written consent.

Preoperative Evaluation

At their appointments, participants provided the following information: name, age, gender, dental history, and preoperative expectations. Preoperative expectations were rated on a numerical Likert scale from 1 to 5, where 1 indicated ‘not concerned about the symptom’ and 5 indicated ‘definitely concerned about the symptom’. Several studies support the direct relationship between dental concern and pain expectations (e.g. Klages, Ulusoy, Kianifard, & Wehrbein, 2004; Morton, Watson, El-Deredy, & Jones, 2009).

The independent variable of this study, preoperative expectations of pain, was an aggregate score of the patients' Likert scale ratings on pain, jaw pain, and discomfort. A score of 3 was the lowest possible count, indicating no concern/expectation toward feeling pain, whereas a score of 15 was the highest, indicating definite concern/expectation toward feeling pain.

Surgical Procedure

The same oral surgeon, in the same operating room and under similar conditions, performed all of the third molar extractions. Following the surgery, the oral surgeon filled out a form detailing the procedure, including the number of teeth extracted, type of anesthesia used, duration (defined as time from the start of the surgery until the last suture), analgesics and antibiotics prescribed, and difficulty of the extraction per tooth assessed by the modified Pederson Difficulty Index for Removal of Impacted Third Molars (Koerner, 1994; Yuasa et al., 2002). Each extracted third molar was given an individual difficulty score, and an average was computed based on the difficulty and amount of teeth removed per person. The modified Pederson Difficulty Index has been tested for validity and reliability (Yuasa et al., 2002) and is presented in Appendix B.

All patients were given routine postoperative instructions and guidelines.

Postoperative Evaluation

For three days following the extraction, participants were instructed to complete an online postoperative assessment (using the LimeSurvey© web-based application tool), which included a modified version of the Postoperative Symptom Severity Scale (PoSSe). Each PoSSe question followed a multiple-choice (closed) format where respondents were only able to indicate one option. The answers to each question received a corresponding score. The scores represented a percentage, whereby a patient completing the questionnaire and answering the most severe category for each question would score a total of 100% and a patient answering the least severe category for each question would score a total of 0%. While the PoSSe has been tested for validity and reliability

and has been used in several third molar studies (e.g. Grossi et al., 2007; Kanatas & Rogers, 2010; Ruta et al., 2000), the modified version, accommodating a daily time frame as opposed to weekly, has yet to be tested. It is presented in Appendix C.

The current study limits the analysis to two PoSSe questions: "Thinking of the past day, for how many hours did you experience pain from your operation?" and "Thinking of the past day, how badly did the pain affect your life?" Only scores on the first day following the extraction (i.e. 24 hours post-surgery) were assessed.

Data Analysis

We performed statistical analyses using Stata (Stata/IC 11.2; StataCorp LP, TX). We assessed psychological, demographic, anatomic, and operative factors in our regression models. Psychological factors consisted of preoperative pain expectations (treated as a continuous variable because such a model gives the advantage of not losing any information), history of prior tooth extraction (a factor likely to influence expectations, and derived from a yes or no response), and the presence or absence of the psychological intervention, which had been randomly assigned to the participants.

Demographic factors included age and gender, which were derived from the patients' reported age at the time of extraction and their indicated gender (either male or female). The anatomical factor considered number of third molars extracted, a categorical variable ranging from 1-4. Difficulty of the extraction and operation time encompassed the operative factors and were continuous variables derived from the oral surgeon's recordings after each operation. Surgeon expertise and anesthetic technique, variables included in prior research, were excluded from our model since the design of our experiment controlled for these factors, as the same surgeon performed all extractions using the same anesthetic technique of general and local anesthesia.

To accommodate our data with the statistical analyses performed, we created dummy variables for condition, history of extraction, sex, and number of teeth removed (a multinomial dummy variable). In creating these necessary dummy variables, we decided to use 'no intervention', 'no history', 'male', and 'four teeth' as the reference categories for intervention condition, previous teeth extractions, gender, and number of third molars extracted, respectively.

Ordinary least square (OLS) regression models were computed to determine the contributory value of the psychological, demographic, anatomic, and operative factors in assessing the level of postoperative pain. Most authors recommend using the rule of thumb of including one explanatory/control variable per ten observations (at most 1:5) in a regression model, otherwise the estimates of the regression line risk the chance of becoming unstable and non-replicative (Carmichael, 2012). For this reason, we were required to limit each model to 3-6 explanatory and control variables and therefore performed five preliminary regressions before generating the best model.

Our main theoretical concern involved psychological factors, so we began with an assessment of these variables. Model 1 included preoperative expectations, intervention and prior extraction history. Model 2 assessed the demographic variables of age and gender. Model 3 considered the anatomic variable of how many teeth were extracted. Model 4 measured the operative variables of difficulty and length of procedure. Model 5 retained all prior significant and reportable factors to see how the variables that seemed to be most important affected postoperative pain. We then integrated Model 5 from each of the PoSSe questions, which generated Model 6, the "best" (most specified) model. We proceeded to record unstandardized and standardized (beta value) regression coefficients.

Assumptions of OLS regression were tested, including normality (skewness≈0, kurtosis≈3), non-colinearity (correlation matrix and VIF), specification error (ovtest), and homoskedasticity (hettest). We assumed variable reliability, independence, and linearity based on theory. Certain models (Q1:

Models 1,2,3,5,6; Q2: Model 1,6) were corrected for heteroskedasticity using White's (1980) correction model.

Results

Variable means and distributions

Descriptive statistics were computed for all study variables (see Table 2).

Table 2. Descriptive Statistics of the Independent and Dependent Variables

Variable	Mean	Standard Deviation	Percent (%)	Range
Psychological				
Preoperative expectations	3.58	1.24		3-15
Intervention				
No			50	
Yes			50	
History of extraction				
No			84.21	
Yes			15.79	
Demographic				
Age (years)	21.74	3.06		18-28
Male			55.26	
Female			44.74	
Anatomic				
Number of teeth extracted				
One			7.89	
Two			13.36	
Three			10.53	
Four			68.42	
Operative				
Difficulty	5.19	1.46		1.67-8
Operation time (minutes)	43.16	11.59		10-60
Outcome Variables				
Question #1	3.73	3.02		0-9.5
Question #2	0.80	0.77		0-2.2

Multivariate analyses

Preliminary Models

Question #1:

Table 3 presents the findings from the OLS regression for the question "Thinking of the past day, for how many hours did you experience pain from your operation?"

The results in the initial equation (Model 1) showed that those with worse expectations experienced significantly more pain following a third molar extraction ($t(3, 34)=3.10$, $p<0.01$) while controlling for intervention and prior tooth extraction. Every unit increase in negative expectations increased pain scores by 0.432 points. Although not significant within our 95% confidence intervals, intervention status was a reportable finding ($t(3,34)=-1.95$, $p=0.06$). History of extraction did not appear to be important in this preliminary model.

The second model (Model 2) testing the demographic variables showed that after controlling for gender, age helped to predict postoperative pain ($t(2,35)=2.03$, $p<0.05$), where every additional year increased pain experienced by 0.285 points on the PoSSe. Gender did not appear to be important in this model.

Model 3 examined the impact of number of teeth extracted on postoperative pain. Here we see that having three teeth removed is significantly less painful than having four removed ($t(3,34)=-2.13$, $p<0.05$). Having one or two teeth removed in comparison to four did not appear to be important in this model.

The fourth model, assessing operative variables, showed that difficulty of extraction and length of the procedure were not significant determinants of post-extraction pain. Length of the procedure, however, was a reportable finding ($t(2,35)=1.97$, $p=0.057$).

Model 5 retained all of the significant and reportable variables from the prior models, which included preoperative expectations, intervention status, age, having three teeth removed referenced against having one, two or four removed (a change in reference as performed in Model 3 because of the unexpected finding that having one and two teeth removed was equivalent to having four teeth removed, yet having three teeth removed compared to four caused less pain), and length of the procedure. Preoperative expectations and having three teeth removed remained significant ($t(6,31)=2.60$, $p<0.01$ and $t(6,31)=-2.12$, $p<0.05$) after controlling for the other variables, and intervention status remained a reportable finding ($t(6,31)=-1.95$, $p=0.06$).

Question #2:

Table 4 presents the findings from the OLS regression for the question "Thinking of the past day, how badly did the pain affect your life?" The same preliminary models as described above were run to determine risk factors for this PoSSe score. Model 1 showed similar findings: the lives of those with worse preoperative expectations were significantly more affected by pain ($t (3, 34)=4.43$, $p<0.001$) while controlling for intervention and prior tooth extraction. The second model demonstrated that age and gender helped to predict how badly pain affects one's life, where every additional year increased PoSSe scores by 0.074 points and being a female increased the score by 0.589 points ($t (2, 35)=1.99$, $p<0.05$ and $t (2, 35)=2.01$, $p<0.05$). The third model showed that the number of teeth removed was not an important factor after controlling for the other variables. Model 4 revealed that length of the procedure had a significant effect on the PoSSe score, where every unit increase in time increased the score by 0.024 points ($t(2,35)=2.23$, $p<0.05$) when controlling for difficulty. Model 5 retained all of the significant variables from the prior models, which included preoperative expectations, age, gender, and length of the procedure. Preoperative expectation was the only factor to retain its significance after controlling for the other variables ($t(4,33)=3.41$, $p<0.01$).

Table 3. Standard Regression Table for Question #1

(PoSSe #9)	**Model 1**[a]	**Model 2**[a]	**Model 3**[a]	**Model 4**	**Model 5**[a]	**Model 6**[a] b	Beta
Psychological Variables							
Preop expectations	0.432** (0.139)	--	--	--	0.377** (0.132)	0.348** (0.133)	0.366
Intervention (1=yes)	-1.641^{+} (0.843)	--	--	--	-1.645^{+} (0.848)	-1.670* (0.840)	-0.285
History of extraction (1=yes)	1.781 (1.336)	--	--	--	--	--	--
Demographic Variables							
Age	--	0.285* (0.140)	--	--	0.210 (0.134)	0.204 (0.133)	0.207
Gender (1=female)	--	1.270 (0.994)	--	--	--	0.518 (0.873)	0.086
Anatomic Variables							
# of teeth extracted							
(1=1 tooth)	--	--	0.295 (2.781)	--	--	--	--
(1=2 teeth)	--	--	2.143 (1.694)	--	--	--	--
(1=3 teeth)	--	--	-1.598* (0.749)	--	-1.647* (0.777)	-1.484 (0.802)	-0.155
Surgical Variables							
Difficulty	--	--	--	-0.105 (0.333)	--	--	--
Operation time	--	--	--	0.082^{+} (0.042)	0.029 (0.044)	0.032 (0.042)	0.121
Constant	0.181 (1.346)	-3.038 (0.994)	3.383 (0.514)	-0.105 (0.333)	-4.651 (3.078)	-4.558 (3.102)	
R^2	0.344	0.134	0.162	0.100	0.428	0.434	
Number of Cases	38	38	38	38	38	38	

Note: **Model 1**, **Model 2**, **Model 3, Model 4,** and **Model 5** are preliminary models; **Model 6** is the final one.
The dependent variable is the score from the question "Thinking of the past day, for how many hours did you experience pain from your operation?"
'No intervention', 'no history', 'male', and 'four teeth' are the reference categories for intervention condition, previous teeth extractions, sex, and number of third molars extracted, respectively.
[a] Model is corrected for heteroskedasticity using White's correction
Standard errors are in parentheses
$^{+}$ demarcates a non-significant yet reportable finding
* $P \leq 0.05$
** $P \leq 0.01$
*** $P \leq 0.001$

Table 4. Standard Regression Table for Question #2

(PoSSe #15)	**Model 1**[a]	**Model 2**	**Model 3**	**Model 4**	**Model 5**	**Model 6**[a] b	Beta
<u>Psychological Variables</u>							
Preop expectations	0.134*** (0.030)	--	--	--	0.113** (0.033)	0.986** (0.033)	0.403
Intervention (1=yes)	-0.309 (0.201)	--	--	--	--	-0.362[+] (0.192)	-0.237
History of extraction (1=yes)	0.280 (0.264)	--	--	--	--	--	--
<u>Demographic Variables</u>							
Age	--	0.074* (0.037)	--	--	0.059 (0.034)	0.051 (0.033)	0.203
Gender (1=female)	--	0.589* (0.226)	--	--	0.363 (0.203)	0.379 (0.198)	0.217
<u>Anatomic Variables</u>							
# of teeth extracted							
(1=1 tooth)	--	--	0.275 (0.477)	--	--	--	--
(1=2 teeth)	--	--	0.055 (0.382)	--	--	--	--
(1=3 teeth)	--	--	-0.55 (0.420)	--	--	-0.412 (0.311)	-0.166
<u>Surgical Variables</u>							
Difficulty	--	--	--	-0.026 (0.084)	--	--	--
Operation time	--	--	--	0.024* (0.011)	0.011 (0.009)	0.010 (0.009)	0.156
Constant	-0.359 (0.283)	-3.038 (2.950)	0.825*** (0.153)	-0.0867 (0.622)	-2.176** (0.748)	-1.647* (0.763)	
R^2	0.381	0.134	0.064	0.125	0.487	0.553	
Number of Cases	38	38	38	38	38	38	

Note: **Model 1**, **Model 2**, **Model 3, Model 4** and **Model 5** are preliminary models; **Model 6** is the final one.
The dependent variable is the score from the question "Thinking of the past day, how badly did the pain affect your life?"
'No intervention', 'no history', 'male', and 'four teeth' are the reference categories for intervention condition, previous teeth extractions, sex, and number of third molars extracted, respectively.
[a] Model is corrected for heteroskedasticity using White's correction
Standard errors are in parentheses
[+] demarcates a non-significant yet reportable finding
* $P \leq 0.05$
** $P \leq 0.01$
*** $P \leq 0.001$

Best Model

To create the best model for the two PoSSe questions, we retained the variables from each Model 5. The best model, Model 6, therefore included the following: preoperative expectations, intervention status, age, gender, having three teeth extracted, and length of the procedure.

Question #1:

We now see that in this more accurately specified model, preoperative expectations and intervention status are the only significant determinants of postoperative pain. Every unit increase in expectations increased postoperative pain scores by 0.348 ($t(6, 31)=2.62$, $p<0.01$) and being in the intervention group decreased pain scores by 1.696 ($t(7,30)=-2.02$, $p<0.05$), when controlling for the other variables.

The coefficient of determination (R^2) or, "goodness-of-fit" of the model was 0.434, meaning 43.4% of the variation in postoperative pain could be explained by the variables in this model. Standardized coefficients demonstrated that preoperative expectations (beta=0.366) were the largest contributor to the variation in pain.

Question #2

The regression of this specified model revealed that preoperative expectation was the only statistically significant determinant of post-extraction pain affecting patients' lives ($t(6, 31)=3.00$, $p<0.01$), where every unit increase in expectation increased the PoSSe score by 0.103. The presence or absence of receiving the intervention was not significant within our 95% confidence intervals, however it was reportable ($t(6, 31)=-1.89$, $p=0.069$). Although not statistically significant, the finding demonstrated a difference between those who received the standard

or modified informed consent, with the latter experiencing a – perhaps clinically* – enhanced recovery.

The coefficient of determination (R^2) of the model was 0.553, meaning 55.3% of the variation in how badly pain affected patients' lives could be explained by the variables in this model. Standardized coefficients demonstrated that preoperative pain expectation (beta=0.403) was the largest contributor to the variation in pain affecting patients' lives.

Discussion

Our findings suggest that preoperative expectations are the strongest predictor of post-extraction pain even after controlling for all other suspected variables that may lead to pain, which supports our first hypothesis. While much has been written about the risk factors of third molar recovery, little has been published on patients' expectations as a possible determinant of therapeutic outcome, i.e. expectation – a confounding variable – has rarely been controlled for. The tremendous variability in others' findings may be explained by this oversight.

The role expectations play in recovery may be explained by a theory put forth by Kirsch (1985) about response expectancies, a term defined as "the anticipation of nonvolitional, subjective, and behavioral responses to particular situational cues" (Kirsch, 1985). In other words, response expectancy is the anticipation of one's own automatic reactions to various behaviors and situations. For example, a person may expect to feel more alert after drinking a cup of coffee (even – if unknowingly – it is decaffeinated) or to feel less pain after taking pain medication (Kirsch, 1997). In this case, patients who expect to feel pain experience more pain compared to those who expect to feel no, or less, pain.

* In clinical studies, it is important to consider the difference between clinical significance and statistical significance. Clinical significance represents a meaningful change in the symptomatic state of functioning of an individual patient whereas statistical significance represents a measure of whether an observed difference is larger or smaller than would be expected to occur by chance alone (Raz, 2005).

The present study lends support to the effectiveness of our informed consent intervention. As mentioned earlier, expectancies develop from various avenues, one particularly being from the information relayed to the patient during the informed consent procedure. To counter these negative expectancies that lead to symptom worsening, the informed consent intervention aimed at managing the patient's expectations through positive thinking strategies. The regression analyses in the current study confirm that the intervention has significant effects on recovery, as the severity of postoperative pain can depend on the absence or presence of the intervention. Subjects who received the intervention had a less severe recovery period, which supports our second hypothesis.

Our analysis revealed that out of the factors research previously tested – namely age, gender, number of teeth removed, difficulty of extraction, surgeon experience, anesthetic technique, and operation time – none were significant determinants of postoperative discomfort when controlling for patient expectations and intervention status. This was an unexpected yet powerful finding, illustrating that the investigated demographic, anatomic, and operative factors have no significant influence on post-extraction pain.

Limitations

There were certain limitations to this study. First, expectation was evaluated through patient concern, which can be interpreted by the lay public as expectation, fear, anxiety, or worry. To date, empirical research supports the direct relationship between dental concern and expectations. For example, Klages et al. (2004) investigated the prediction of anticipated pain and pain actually experienced in stressful dental procedures by patients' trait anxiety and pain sensitivity. Patients who indicated high dental fear expected more affective, sensory and intense pain compared to low dentally fearful individuals. Further, they found that highly dentally anxious patients reported suffering more pain compared to the low fearful patients (Klages et al., 2004). Their results substantiate that rating patient concern is a suitable proxy for measuring

expectation; nonetheless, changing the wording of the question to directly assess expectations would have strengthened our study.

Second, the informed consent intervention study from which this analysis was derived assessed pain scores 24, 48, and 72 hours post-extraction using three different instruments. It was beyond the scope of this article to consider the three time points, as well as results from the other two pain assessments. Moreover, although the original PoSSe has been tested for reliability and validity, the modified version looking at a more specific time frame has not. Additionally, the independent variable, the aggregate score of preoperative expectations, has not been tested for these measures. Future studies should take this into consideration and test their reliability and validity. Nevertheless, looking at two separate pain questions on the PoSSe and attaining similar results strengthened our confidence in the findings.

Third, postoperative pain cannot be completely explained by the presented model because of the small sample size (n=38). Following the rule of including one factor per five-to-ten observations, we were required to limit each model to three-to-six variables. Had the sample size been larger, we would have been able to include all variables in the fully specified regression model. Therefore, further research involving a larger cohort is needed to determine a more exhaustive predictive model for postoperative pain after wisdom teeth removal.

Our small sample size, however, was justifiable by its uniqueness, as more control was achieved in several ways. Firstly, all of the patients were healthy young adults and were non-smokers. Secondly, the same oral surgeon under similar operative procedures in the same clinic performed all of the extractions. This eliminated, or at least greatly reduced variability in expertise, surgical technique, and use of anesthesia. Nonetheless, as a consequence, we must be cautious when generalizing the results to other practices. Ideally, future studies should be conducted across a number of clinics, both within public and private sectors.

Conclusion

The findings presented in this study challenge claims of the determinants of postoperative pain. We revealed that expectations are a highly important consideration in predicting therapeutic outcome, whereas demographic, anatomic, and operative variables are non-significant risk factors. While our analysis focused on third molar extractions, it provided reason to believe that recovery from many medical and dental procedures depend on this psychological variable. Unlike demographic, anatomic, and certain operative variables, healthcare practitioners can actually help modify patient expectations. Future research should therefore investigate how preoperative expectancies affect healing in all healthcare disciplines, as findings can have important implications for designing and administering treatments and implementing prevention strategies.

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General Discussion

The present thesis aimed to unravel the psychological corollaries of the informed consent discussion. In the literature review, we deconstructed this standard-of-care tool to understand its origins, intentions, and implications. Looking into the disclosure of risks and side effects, we discovered that the negative expectancies patients form hinder their therapeutic outcome through a nocebo effect. Accordingly, we recognized that contemporary healthcare faces an ethical dilemma: current practice unintentionally threatens the bioethical principle of non-malfeasance to uphold patient autonomy. Researchers have offered potential solutions to this issue, such as tailoring the process to match specific informational needs of the patient (Agard, 2005) or providing a short consent form with optional appendices detailing all other pertinent information (Wood et al., 2001). Nevertheless, the majority of these suggestions risks eroding certain ethical ideals of the consent process. We therefore offered a novel and realistic model of informed consent, responding directly to the profound dilemma between respecting patient autonomy while upholding the physician's duty to do no harm. We recommended an approach that would not only mitigate the nocebo effect, but would also promote a placebo effect, allowing the informed consent process to dually serve as an ethical requisite in the clinical milieu as well as an autonomous, therapeutic intervention.

In our experimental piece, we translated theory into practice by testing the effectiveness of using the informed consent procedure as an intervention. Using wisdom teeth extractions as a lens, we discovered that modifying the consent process – by providing not only specific treatment details but also information about psychological mechanisms involved in recovery – enhanced patients' therapeutic outcomes. A reduction in post-operative pain was the strongest finding, including how pain affected one's post-operative quality of life. Further, our results indicated that analgesic consumption during the recovery period decreased for the patients who participated in the modified consent process.

In the third text, we performed additional statistical analyses on the data collected in the prior study to explore the risk factors of postoperative third molar removal pain. Primarily, we focused on the importance of preoperative expectations in determining pain. Our results demonstrated three main findings: 1) that out of all independent factors, expectation was the greatest predictor of the severity of pain; 2) that the modified consent contributes to better recovery compared to standard practice; and 3) that demographic, anatomic, and operative variables are non-significant determinants of pain when taking expectations into account.

The findings from this thesis have profound implications for current healthcare. One of the essential functions of modern medicine is to foster and uphold high standards of care in the delivery of health services (Agard, 2005). Herein, we have shown that tailoring the informed consent process to include an explanation of certain psychological mechanisms of recovery is beneficial to patients. It follows, therefore, that implementing such an intervention becomes an ethical imperative; otherwise practitioners fail to provide optimal care. Familiarity with such research findings will be of value to all those working in areas involving informed consent, including but not limited to: medicine, mental health care, nursing, dentistry, biomedical research, biomedical ethics, and law. Educating those who develop and provide informed consent will help advance knowledge and understanding of the ethical and psychological underpinnings of the informed consent process, and allow healthcare professionals to optimize treatment outcomes for their patients.

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Appendix A

Preoperative Questionnaire

(page 1 of 2)

The preoperative questionnaire assessing inclusion/exclusion criteria and current concerns towards WTE postoperative complications.

Patient Preoperative Questionnaire:

This questionnaire aims to gather some information about you and your expectations with regard to your wisdom tooth extraction procedure. Please answer the questions as accurately as possible.

Please provide your first and last name _____

Please provide your email _____

1. Please indicate your age
   a. 18-28 b. Other

2. Please indicate your sex
   a. Male b. Female

3. Please indicate if you are currently diagnosed with a severe medical or mental illness
   a. Yes b. No

   If yes, which? _____

4. Please indicate if you are a smoker
   a. Yes b. No

5. Please indicate how often you consume alcoholic beverages
   a. Seldom b. Monthly c. Weekly d. Daily
   e. Other: _____

6. Please indicate how often you drink coffee
   a. Seldom b. Monthly c. Weekly d. Daily
   e. Other: _____

7. Please indicate how often you drink warm beverages (ex: hot water, tea, soup, etc)
   a. Seldom b. Monthly c. Weekly d. Daily
   e. Other: _____

8. Please indicate how often you drink cold beverages (ex: ice water, soda, etc)
   a. Seldom b. Monthly c. Weekly d. Daily
   e. Other: _____

Appendix A

Preoperative Questionnaire

(page 2 of 2)

9. Do you have a history of oral surgery?
   a. Yes b. No

   If yes, please explain:

   _____

10. Have you previously experienced trauma to the mouth?
    a. Yes b. No

    If yes, please explain:

    _____

Please rate your concerns towards the following symptoms (1=weakest, 5=strongest)

1. Anesthetics/Medications during procedure	1---2---3---4---5
2. Discomfort and sensitivity	1---2---3---4---5
3. Swelling	1---2---3---4---5
4. Bruising	1---2---3---4---5
5. Pain	1---2---3---4---5
6. Bleeding	1---2---3---4---5
7. Numbness or tingling to the lip, chin or tongue	1---2---3---4---5
8. Infection	1---2---3---4---5
9. Additional Procedures as a result of infection	1---2---3---4---5
10. Jaw pain	1---2---3---4---5
11. Sinus abnormalities	1---2---3---4---5
12. Jaw or alveolar bone fracture	1---2---3---4---5
13. Damage to adjacent teeth or restorations	1---2---3---4---5

Appendix B

Surgeon Questionnaire

(page 1 of 2)

Surgeon questionnaire and the modified version of Pederson's difficulty index scale for removal of impacted third molars assessing the complexity of the surgical procedure

Patient Name: _____

Questionnaire for oral surgeon:

1. How many wisdom teeth were extracted?

   1 2 3 4
2. What were their locations?

   18 28
   38 48

3. Was the patient intravenously sedated?
   Yes No

4. What kind of anesthetic was used?

   Local General IV Sedation Other

5. Were analgesics prescribed to the patient?
   Yes No

6. If yes, what was prescribed? (Please include dose)

   Ibuprofen 600 Percocet Other: _____

7. Were antibiotics prescribed to the patient?
   Yes No

8. If yes, what was prescribed? (Please include dose)

   Amoxcillin 500 Biaxin 500 Other: _____

9. Length of procedure: _____

10. Were there any complications during the procedure?
    Yes No

    If yes, please elaborate _____

Appendix B

Surgeon Questionnaire

(page 2 of 2)

Pederson Difficulty Index for Removal of Impacted Third Molars (modified)
Please circle the appropriate numbers

18		**28**	
Depth:		Depth:	
Level A: high occlusal level	1	Level A: high occlusal level	1
Level B: medium occlusal level	2	Level B: medium occlusal level	2
Level C: deep occlusal level	3	Level C: deep occlusal level	3
Ramus relationship/space available:		Ramus relationship/space available:	
Class 1: sufficient space	1	Class 1: sufficient space	1
Class 2: reduced space	2	Class 2: reduced space	2
Class 3: no space	3	Class 3: no space	3
Width of root:		Width of root:	
Thin or thick (multiple roots)	1	Thin or thick (multiple roots)	1
Bulbous	2	Bulbous	2
38		**48**	
Depth:		Depth:	
Level A: high occlusal level	1	Level A: high occlusal level	1
Level B: medium occlusal level	2	Level B: medium occlusal level	2
Level C: deep occlusal level	3	Level C: deep occlusal level	3
Ramus relationship/space available:		Ramus relationship/space available:	
Class 1: sufficient space	1	Class 1: sufficient space	1
Class 2: reduced space	2	Class 2: reduced space	2
Class 3: no space	3	Class 3: no space	3
Width of root:		Width of root:	
Thin or thick (multiple roots)	1	Thin or thick (multiple roots)	1
Bulbous	2	Bulbous	2

Difficulty Index

Very difficult	7-8
Moderately difficult	5-6
Slightly difficult	3-4

Difficulty Index:
18: _____
28: _____
38: _____
48: _____

Appendix C

Postoperative Assessment

(page 1 of 6)

Postoperative questionnaires assessing pain and symptom severity

Postoperative Patient Questionnaire:

This questionnaire aims to assess your recovery from your wisdom tooth extraction procedure. Please answer the questions as accurately as possible.

Numerical Rating Scale for Pain

Please indicate how much pain you are feeling (0=no pain, 10=worst pain imaginable)

0-----1-----2-----3-----4-----5-----6-----7-----8-----9-----10

Are you currently taking medication to treat wisdom tooth extraction symptoms (i.e. pain, swelling, etc)?

a. Yes b. No

If yes, what medications are you taking?

_____

And how often? (*as prescribed = either by surgeon or by directions on bottle)*

a. As prescribed

b. More than prescribed

c. Less than prescribed

d. Other: _____

Appendix C

Postoperative Assessment

(page 2 of 6)

McGill Pain Questionnaire

What Does Your Pain Feel Like?

Some of the following words below describe your **present** pain. Only choose those words that best describe it. Leave out any category that is not suitable. Use only a **single** word in each appropriate category - the one that applies best.

1:	flickering	7:	hot	14:	punishing
	quivering		boring		grueling
	pulsing		scalding		cruel
	throbbing		searing		vicious
	beating				killing
	pounding				
		8:	tingling	15:	wretched
2:	jumping		itchy		blinding
	flashing		smarting		
	shooting		stinging	16:	annoying
					troublesome
		9:	dull		miserable
3:	pricking		sore		intense
	boring		hurting		unbearable
	drilling		aching	17:	spreading
	stabbing		heavy		radiating
	lancinating				penetrating
					piercing
		10:	tender		
4:	sharp		taut	18:	tight
	cutting		rasping		numb
	lacerating		splitting		drawing
					squeezing
					tearing
5:	pinching	11:	tiring		
	pressing		exhausting	19:	cool
	gnawing				cold
	cramping				freezing
	crushing	12:	sickening		
			suffocating	20:	nagging
					nauseating
6:	tugging				agonizing
	pulling	13:	fearful		dreadful
	wrenching		frightful		torturing
			terrifying		

Appendix C

Postoperative Assessment

(page 3 of 6)

McGill Pain Questionnaire (continued)

How Strong is Your Pain?

People agree that the following 5 words (mild discomforting distressing horrible excruciating) represent pain of increasing intensity. Choose the most appropriate word for the following questions.

Question

Which word describes your pain right now?
- mild
- discomforting
- distressing
- horrible
- excruciating

Which word describes it at its worst?
- mild
- discomforting
- distressing
- horrible
- excruciating

Which word describes it when it is least?
- mild
- discomforting
- distressing
- horrible
- excruciating

Which word describes the worst toothache you ever had?
- mild
- discomforting
- distressing
- horrible
- excruciating

Which word describes the worst headache you ever had?
- mild
- discomforting
- distressing
- horrible
- excruciating

Which word describes the worst stomachache you ever had?
- mild
- discomforting
- distressing
- horrible
- excruciating

Appendix C

Postoperative Assessment

(page 4 of 6)

Modified Postoperative Symptom Severity Scale (PoSSe)

Please indicate your best response per question.

EATING

1. In the last day, has your operation affected your **enjoyment** of food?
   - [0] No, not at all
   - [5.25] Yes, a little
   - [10.5] Yes, very much

2. In the last day, how often were you **unable to open your mouth** normally because of your operation?
   - [0] None at all
   - [2.63] 1-2 hours
   - [5.25] 3-4 hours
   - [7.88] 5-6 hours
   - [10.5] 7+ hours

SPEECH

3. In the last day, for how many hours was your **voice** affected because of your operation?
   - [0] None at all
   - [1.25] 1-2 hours
   - [2.5] 3-4 hours
   - [3.75] 5-6 hours
   - [5] 7+ hours

4. At the worst time of the day, how badly was your **speech** affected by your operation?
   - [0] None at all
   - [1.25] 1-2 hours
   - [2.5] 3-4 hours
   - [3.75] 5-6 hours
   - [5] 7+ hours

SENSATION

5. Thinking of the past day, for how many hours were your lips or tongue feeling **tingling** because of your operation?
   - [0] None at all
   - [2] 1-2 hours
   - [4] 3-4 hours
   - [6] 5-6 hours
   - [8] 7+ hours

6. Thinking of the past day, for how many hours were your lips or tongue feeling **numb** because of your operation?
   - [0] None at all
   - [2] 1-2 hours
   - [4] 3-4 hours
   - [6] 5-6 hours
   - [8] 7+ hours

Appendix C

Postoperative Assessment

(page 5 of 6)

Modified PoSSe (continued)

APPEARANCE

7. Thinking of the past few days, for how many days were your face and/or neck **bruised** because of your operation?

[0] None at all
[1.5] 1-2 hours
[3] 3-4 hours
[4.5] 5-6 hours
[6] 7+ hours

8. Thinking of the past day, for how many hours were your face and/or neck **swollen** because of your operation?

[0] None at all
[1.5] 1-2 hours
[3] 3-4 hours
[4.5] 5-6 hours
[6] 7+ hours

PAIN

9.Thinking of the past day, for how many hours did you experience **pain** from your operation?

[0] None at all
[2.38] 1-2 hours
[4.75] 3-4 hours
[7.13] 5-6 hours
[9.5] 7+ hours

10. Thinking of the past day, has the pain from your operation been controlled by **painkillers?**

[0] I have had no pain
[2.38] Yes, completely controlled
[4.75] Controlled mostly but still some discomfort
[7.13] Poorly controlled
[9.5] Not controlled at all

SICKNESS

11. Thinking of the past day, for how many hours did you **vomit** of **feel nauseated**?

[0] None at all
[1.25] 1-2 hours
[2.5] 3-4 hours
[3.75] 5-6 hours
[5] 7+ hours

12. At the worst time of the day, **how many times** did you vomit or feel nauseated?

[0] Not at all
[1.25] Once
[2.5] 2-3 times
[3.75] More than 3 times
[5] All the time (all day long)

Appendix C

Postoperative Assessment

(page 6 of 6)

Modified PoSSe (continued)

INTERFERENCE WITH ACTIVITIES

13. In the last day, did the operation prevent you from carrying out **work/housework** and **other daily activities**?

[0] No, not at all
[0.83] I could continue with my work, but my work suffered
[1.65] Yes, for 1 hour
[2.48] Yes, for 2-6 hours
[3.3] Yes, for more than 7 hours

14. In the last day, have your **leisure activities** been affected by your operation? (including hobbies and social life)

[0] Not affected by the operation
[0.83] Mildly affected by the operation
[1.65] Moderately affected by the operation
[2.48] Severely affected by the operation
[3.3] The operation prevented any social life at all

15. Thinking of the past day, how badly did the pain affect your life?

[0] Not at all
[1.1] Slightly
[2.2] Moderately
[3.3] Severely

Note: Parentheses indicate the score corresponding to each response. We did not include these scores on the questionnaire given to participants.

Appendix D

Detailed Methodology: Flow of Events

1. The participant is referred to an oral surgeon at the SMBD-JGH for a third molar extraction.
2. The participant calls to make an appointment.
3. The dental secretary asks if the participant is between 18-28 years of age and about their smoking habits. If these screening criteria are fulfilled, the secretary will ask if the participant would like to participate in the study and be contacted by the RazLab. The exclusion criteria of possessing a diagnosis of a severe medical or mental illness is only assessed later on during the preoperative questionnaire.
4. The dental secretary contacts the RazLab with the names and contact information of those who agree to participate.
5. We contact participants and explain the general nature of the experiment. Verbal consent is obtained.
6. The participant gives written consent at extraction appointment, prior to the surgery.
7. The participant fills out the preoperative questionnaire concerning their health. status and current expectations towards WTE postoperative complications
8. We randomly separate participants (by flip of a coin) into 2 groups
    a. Control – listen to an innocuous message
    b. Experimental – listen to a "special message" (the independent variable)
9. The participant undergoes the wisdom tooth extraction. There are no alterations to the actual dental procedure.
10. The oral surgeon fills out the surgeon questionnaire, including the modified Pederson's difficulty index for removal of impacted third molars.
11. At intervals of 24, 48 and 72 hours following the procedure, participants assess clinical and psychological parameters (the dependent variables), which includes questionnaires measuring pain levels and physical symptoms (eating, speech, appearance, sickness, interference with daily activities, etc.), measured by the NRS-11, the McGill Pain Questionnaire, and the modified PoSSe. We contact participants by phone to remind them to complete this online assessment. At the first time point, we send participants a standardized email that provides the website URL and outlines the instructions for questionnaire completion.