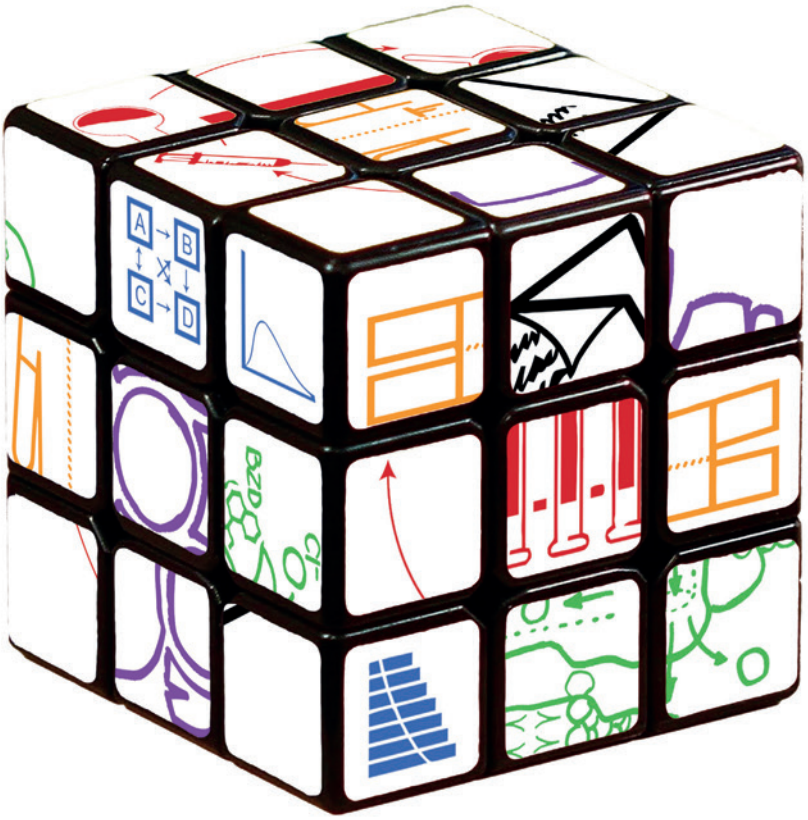
Medical Decision Making in Day-Case Surgery



Hendrik-Jan Mijderwijk

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Hendrik-Jan Mijderwijk

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Voor Marieke
Voor mijn ouders

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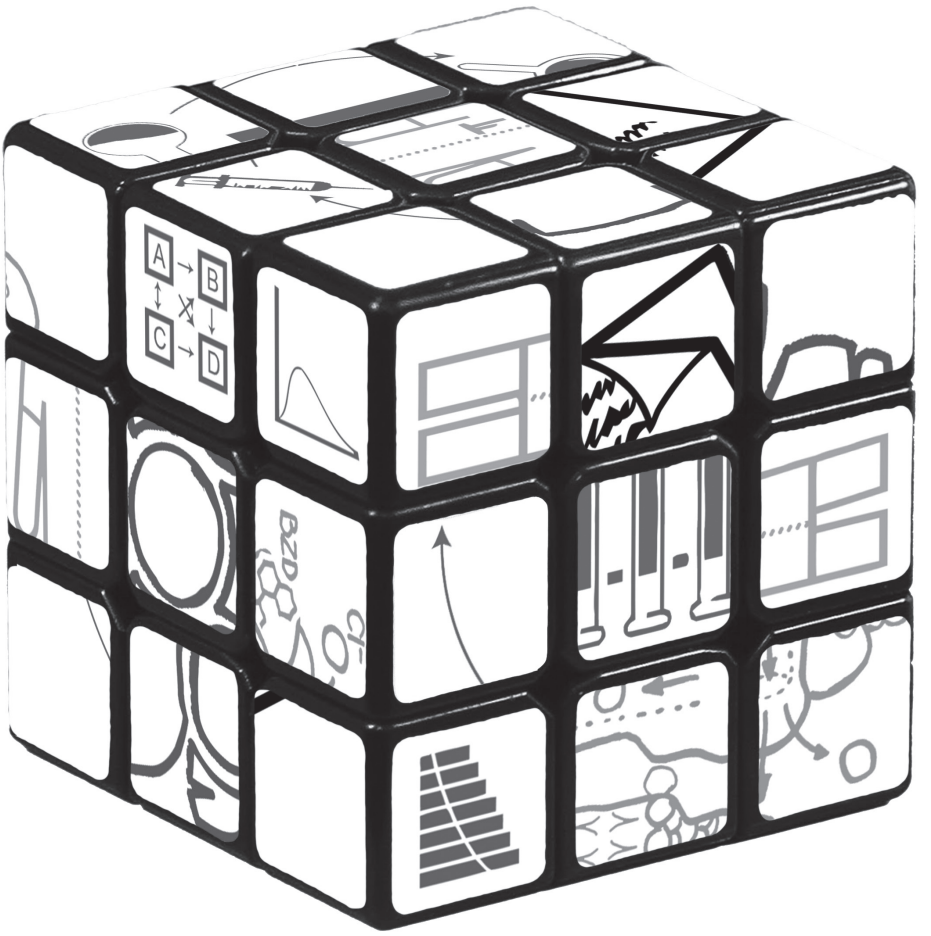
INTRODUCTION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GENERAL INTRODUCTION

CHAPTER 1

Day-case surgery has its origin more than 100 years ago. James H. Nicoll was the first surgeon who operated patients – i.c. children – on a day-case base.[1] In 1909 he published his promising results on nearly 9,000 day-case surgical procedures.[2] It took almost 50 years before other results supported day-case surgery.[3] From that point on, the use of day-case surgery gradually increased. In the USA elective surgery performed in a day-case setting increased from 34% to 61% (1985 – 1994), while in the UK the increase was from 15% to 70% (1989 – 2003).[4] Today, modern day-case surgery is continuously increasing worldwide because – among others – safety has further increased with anaesthetic and surgical advancements – even craniotomies for brain tumour resection have recently been performed in a day-case setting.[5,6]

In day-case surgery patients are admitted and discharged on the day of surgery. A co-founder of the International Association of Ambulatory Surgery proposed an internal definition of a surgical day case as follows: "A surgical day case is a patient who is admitted for investigation or operation on a planned non-residential basis and who nonetheless requires facilities for recovery. The whole procedure should not require an overnight stay in a hospital bed."[7]

Day-case surgery is beneficial is many ways.[4] A couple of them are outlined. From a financial point of view, day-case surgery is cost saving as patients are admitted and discharged on the day of surgery.[4,8,9] As sooner recovery is normally achieved when compared to inpatient surgery, patient's return to normal activities including work will be sooner.[4] From a health care point of view, day-case surgery is safe and reduction in surgical waiting lists may be achieved by the higher turnover.[10,11] In addition, the scheduling can be more efficient as cancellation of surgical procedure due to for example an emergency procedure is rare.[4] From a patient's perspective, the disruption of normal daily living is minimised which is preferred by most patients.[4] Furthermore, hospitalisation is avoided which reduces, for example, the risk of infection and thromboembolism as a result of bedridden.[12,13] Besides these advantages, patients have less contact with health care professionals. Consequently, they have to manage a substantial part of their postoperative recovery in their home situation together with their social network. Therefore, selecting the right patient for day-case surgery requires a proper preoperative evaluation.

1.1. Preoperative evaluation

The preoperative evaluation of the patient is one of the main tasks of anesthesiologists. Adequate evaluation will lead to an appropriate selection of patients and preparation for the surgical procedure. Generally, the preoperative evaluation includes evaluation

of the physical status and evaluation of the psychological status.[14] In day-case surgery, patients are normally physically well, and the evaluation of the psychological status is therefore of substantial interest. The psychological status could be influenced in either a psychologically or pharmacologically way which will be outlined below.

1.1.1. Psychological preparation

Psychological preparation is performed by nursing staff as well as by physicians. At nursing level, psychological preparation may include charts, videos, written and verbal information but should ensure the whole patient experience of the surgical episode.[15] At physician level, psychological preparation is achieved by means of the preoperative visit and interview, and should include an explanation of the anticipated events together with the planned anesthetic regime.[14] The preoperative interview is a powerful method that could enhance the apprehensive attitude of patients and reduction of anxiety.[14] However, unfortunately, psychological preparation is not always sufficient and anesthesiologists necessarily make use of pharmacological preparation.

1.1.2. Pharmacological preparation

Preoperative pharmacological preparation is usually referred as 'premedication'. The main goal of premedication is to relief patients' level of anxiety. In day-case surgery, premedication seems to be a suitable choice for preoperative preparation as patients are normally physically well and contraindications based on physiological reasons or morbidity reasons are rare. Utility of premedication is still inconclusive, however, and can even differ in an institution.[16]

The development of premedication has his roots in the early fifties. Laborit and Huguenard found that chlorpromazine depressed the central nervous system and it was therefore proposed as premedication. Accordingly, other psychopharmaca were introduced over the years. Although several preoperative drugs could serve as an appropriate premedication, the benzodiazepines have been generally used as premedication.[14]

The benzodiazepine history starts with the work done by Leo H Sternbach. In the early 1930s, Sternbach worked with benzheptoxdiazines in order to find new dyestuffs at the University of Cracow, Poland. Although this was an unsuccessful story, he continued working with these compounds in the mid 1950s in order to find better tranquilizers.[17] By chance, Sternbach and his coworkers found a compound that was superior to the existing tranquilizers. This compound had promising anxiolytic properties and was therefore introduced in 1960 under the trademark Librium, generic name Chlordiazepoxide, a

benzodiazepine nowadays.[18] Accordingly, other benzodiazepines were introduced over the years. The benzodiazepine lorazepam was introduced in 1977.[17]

The clinical effects of benzodiazepines are predominantly a consequence of its action in the central nervous system (CNS). Specifically, they cause neural inhibition as they reinforce the effects performed by ɣ-aminobutyric acid (GABA).[19] GABA is a prominent inhibitory neurotransmitter in the brain.[20] Among others, GABA interacts with the $GABA_A$ receptor.[20] The attachment of GABA to the $GABA_A$ receptor leads to an inward flow of chloride (Cl^-) into the neuron inducing hyperpolarization of the neuronal membrane.[20] Consequently, the cell is robust for excitatory neurotransmitters.[20]
Benzodiazepines attach to the $GABA_A$ receptor complex too, but need GABA for its performance – without GABA they cannot open the Cl^- channel.[21] Attachment of a benzodiazepine will lead to an increase of the chloride ion conductance of the postsynaptic membrane which will lead to inhibition of neuronal firing,[19,22] Figure 1. As benzodiazepines act predominantly on the $GABA_A$ receptor, they are barely toxic for other organs outside the CNS, e.g. respiratory and cardiovascular system, especially with dosages used for premedication purposes.[14] This is one of the reasons why benzodiazepines are among the most popular drugs used for premedication.[14] Therefore, this thesis focuses on benzodiazepines.

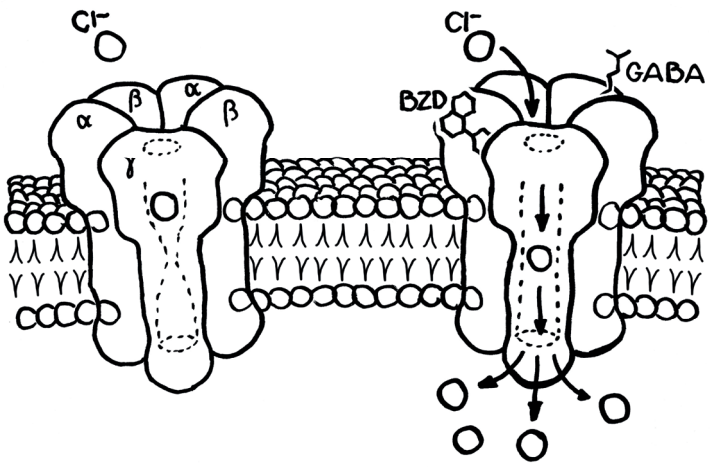

FIGURE 1 | Schematic illustration of the effect of the attachment of benzodiazepines to the $GABA_A$ receptor complex
Abbreviations: Cl^- = chloride; BZD = benzodiazepine; GABA = gamma-aminobutyric acid.

Among the most commonly used benzodiazepines (i.e. midazolam, diazepam and lorazepam), lorazepam is the most anxiolytic, and the most potent.[14,19] This makes lorazepam suitable for premedication in day-case surgery, although some criticisers do not agree because the relatively long half-life of lorazepam can be disadvantageous in day-case surgery. Others even think it is unnecessary to administer benzodiazepines as premedication in day-case surgery due to the nature of the procedure and for concerns of delayed recovery. Almost half of the day-case surgery patients request for premedication nonetheless.[23] Pharmacologically, this thesis focuses on the potent lorazepam. Further details of lorazepam are therefore outlined below.

1.1.2.1 Pharmacokinetics

Absorption—Orally, lorazepam is absorbed from the gastrointestinal tract with peak plasma levels attained within 2 hours.[24] Intramuscularly, absorption of lorazepam is dependent on the blood flow velocity with peak plasma levels attained within 1.5 hour with regards to the deltoid muscle.[24] Intravenously, absorption is redundant; the clinical effects can be observed within several minutes after injection.[25,26]

Elimination—the biotransformation of lorazepam is different from the other benzodiazepines. Lorazepam is biotransformed by direct glucuronide conjugation followed by predominantly renal excretion of the conjugation metabolite,[25] whereas other benzodiazepines also have to undergo phase I reactions.[19] In contrast to other benzodiazepines, the elimination of lorazepam does not involve pharmacologically active metabolic products.[19] Therefore, liver and renal failure have only a minor effect on the pharmacokinects of lorazepam. Also, interactions with other drugs are less likely, but may occur, for example, in the case of rifampicine, valproic acid and clozapine.[27-29]
The mean half-life of lorazepam elimination is 14-15 hours with a range of 8 to 25 hours.[24,30] Other kinetic data with regards to lorazepam include volume of distribution, 1.0 to 1.3 L/kg; and clearance, 0.7 to 1.2 ml/min/kg.[30]

1.1.2.2 Pharmacodynamics

As lorazepam induces depression of the central nervous system, among its pharmacodynamic effects (i.e. clinical effects) are sedation, hypnosis, reduction of anxiety, muscle relaxation, impairment of psychomotor function and anti-convulsant activity.[19,25] From a respiratory and cardiovascular point of view, lorazepam may induce repiratory depression and a depression of the systemic vascular resistance (which results in a lowering of the arterial blood pressure and an increase in heart rate), respectively.[19,25] Furthermore, a small reduction of cardiac output has been reported.[19]

As a premedication, the endeavoured pharmacodynamic actions of lorazepam include reduction of anxiety, anterograde amnesia and (maintenance of) sedation.[25] The pharmacodynamic effects are dose-dependent, and are therefore reversible upon reduction of dosage. Side effects are usually a result of over-dosing and can be derived easily from the pharmacodynamic effects of lorazepam; for example, oversedation, hangover, impaired psychomotor function and drowsiness.

1.1.2.3 Pharmacogenetics

Pharmacogenetics have been defined as the study of genetic variations that cause a variable drug response and includes the genetic polymorphism of drug metabolizing enzymes, drug transporter proteins, and drug receptors.[31] These three aspects will be introduced below together with clinical applications with respect to lorazepam.

1.1.2.3.1 Drug metabolizing enzymes

Important routes of drug metabolism include phase 1 and phase 2 reactions (Figure 2), each utilized with its own specific enzymes. As phase 1 reactions do not apply in the case of lorazepam it is not outlined in further detail. Phase 2 reactions facilitate glucuronidation. Enzymes of interest in our field include uridine 5'-diphosphate-glucuronosyltransferases (UGTs), glutathione *S*-transferase, *N*-Acetyltransferase 2 and sulfotransferases.[31] Among the enzymes of interest, the UGTs are of importance with respect to lorazepam. UGTs are generally divided into two families: the UGT1 family and the UGT2 family.[32] The *UGT2B15* genotype is one of the members of the UGT2 family. Polymorphisms in this genotype have been shown to be of clinical interest, accounting for more than half of the total clearance of lorazepam.[33] Pharmacodynamics, such as sedation and psychomotor function, are also affected by *UGT2B15* polymorphism.[33] The effects on one of the main goals of premedication (i.e. reduction in anxiety) have not been evaluated yet however. Lorazepam is also glucuronidated by *UGT2B7*. However, this genotype has shown to be insufficient to affect the systemic clearance of lorazepam substantially.[34]

1.1.2.3.2 Drug transporters proteins

Another way that could influence drug activity is the velocity of drug absorption. Drug absorption can roughly be either passively (i.e. via diffusion) and actively (i.e. via transporter proteins). Among transporter proteins, membrane transporters play a vital role. Most ABC (adenosine triphosphate (ATP) binding cassette) proteins, one of the largest protein families known, are membrane transporters.[35] Among these membrane transporters, P-glycoprotein is probably the most studied member of the family.

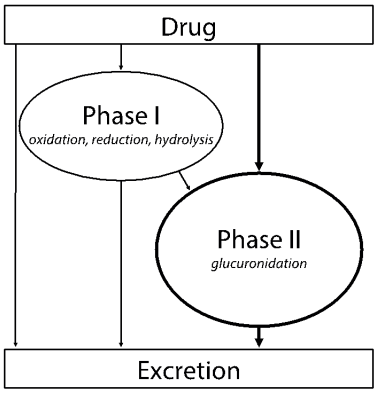

FIGURE 2 | Important routes of drug metabolism

The route of lorazepam is primarily via glucuronidation (bold face). Adapted with permission from de Wildt SN, et al. Glucuronidation in Humans. Pharmacogenetic and developmental aspects. Clin Pharmacokinet. 1999;36:439-452.

P-glycoprotein is expressed, for example, on the membrane of the intestine and tubules of the kidney but also at the blood-brain barrier (BBB),[35] and is responsible for transport of many substrates out of cells.[36] The BBB has to protect the brain and CNS from toxic substances, like drugs. P-glycoprotein therefore plays an essential role in maintaining the homoeostasis in the CNS: high and low P-glycoprotein levels at the BBB may result into too low or too high concentrations of the drug in the brain, respectively.[37] Concerning lorazepam the influence of P-glycoprotein levels is not intensively studied, although some reports suggest clinical significance.[38,39] Another member of the ABC family that might be of interest in our field is the multi-drug resistance-associated proteins (MRPs).[31,40]

1.1.2.3.3 Drug receptors

Pharmacogenetically, a third way to explain some of the diversity in drug activity is by polymorphisms that modify drug receptors. Lorazepam attaches to the $GABA_A$ receptor complex. Although there are no reports that describe specific polymorphisms in the $GABA_A$ that affect the activity of lorazepam, there is literature that covers this issue more generally. For example, it is known that, polymorphisms in the $GABA_A$ receptor may result in impaired benzodiazepine insensitivity.[41,42] The clinical significance is inconclusive as other literature does not find such relation.[43]

1.2 Postoperative evaluation in day-case surgery

Although day-case surgery is beneficial in multiple ways, we need to take into account new outcomes where patients may be suffering from when we analyse the quality of day-case surgery. Perioperative morbidity and mortality are extremely low.[44] The actual recovery time in hospital is relatively short and the necessary postoperative care is transferred from health care professionals to the patients themselves together with their social network. The colorally is that postoperative evaluation in day-case surgery has been shifted towards predominantly psychological outcomes including anxiety, depressive moods, aggression and feelings of fatigue. Nevertheless, somatic outcomes should not be ignored. Vulnerable patients according to these outcome parameters should be identified and treatments adapted to the patient's needs should be evaluated. Statistical models could help to achieve these aims.

1.3 Statistical modeling in day-case surgery

Next to the biomedical profession, the profession of biostatistics has made significant progress. Biostatistically, a valuable innovation is the application of Structural Equation Modeling (SEM). Although previously mentioned as an approach that should be further established in anesthesiology,[45] application of this statistical methodology is very rare in this field. With the shift towards predominantly psychological outcomes in day-case surgery, multiple outcomes became of interest that ideally should be analysed jointly. Accordingly, analysis by means of SEM is a powerful and suitable strategy to apply.[46]

1.3.1 Structural Equation Modeling

SEM includes a family of several traditional multivariate statistical analysis techniques.[47] SEM is a statistical methodology that specifies, estimates, and evaluates models of (non) linear relationships among determinants and outcome variables. SEM makes use of observed variables (i.e. variables directly measured) and/or latent variables (i.e. variables indirectly measured). In contrast with multiple regression analysis for observed variables, SEM models could contain many dependent and independent variables that could be either observed or latent variables.[47] An additional advantage of SEM is the possibility to estimate indirect effects (i.e. from variable to mediation variable(s) to another variable) next to direct effects (i.e. from variable to variable). To visualize structural equation models, researchers usually make use of graphical path diagrams. To properly make use of SEM, the statistical assumptions should be taken into account and large sample sizes are desired.[47] Although SEM could be used for many research purposes, SEM is typically useful for testing theories, hypothesis-generating purposes, exploration and when we are interested in several different effects among a set of variables for several different

outcome parameters.[47,48]

1.4 Outline of this thesis

The aim of this thesis was to investigate, in a multidisciplinary way, the effects of premedication on predominantly psychological outcome variables after day-case surgery. Furthermore, the aim was to identify vulnerable patients in the postoperative period by means of prognostic modeling including SEM.

1.4.1 Part 1: Premedication with lorazepam and other benzodiazepines

Part 1 evaluates the preoperative pharmacological preparation (i.e. premedication) provided by the anesthesiologist. **Chapter 2** presents the results of a randomized placebo-controlled clinical trial assessing the effects of lorazepam premedication on the quality of recovery after day-case surgery with specific attention for psychological phenomena. The influence of pharmacogenetic polymorphisms on the most prominent pharmacodynamic action of lorazepam (i.e. anxiety reduction) is investigated in **Chapter 3**. **Chapter 4** comprises (1) a systematic review of the relevant literature assessing the effectiveness of benzodiazepine premedication on postoperative psychological- and somatic outcomes, and (2) a meta-analysis of studies that report on these outcomes.

1.4.2 Part 2: Identifying vulnerable patients

Chapters 5 and 6 show studies using preoperative data in order to identify patients preoperatively that are likely to be vulnerable in the postoperative period. **Chapter 5** shows a prognostic model that enables predicting multiple psychological outcomes simultaneously one week after day-case surgery. The proposed model provides an evidence-based tool for anesthesiologist to determine which patients are likely vulnerable one week after the surgical procedure. In **Chapter 6**, three categories of psychological vulnerability are constructed according to normative data. Subsequently, using preoperative data of the patients, a prediction model was build to identify these postoperative vulnerability categories.

Postoperative fatigue emerges substantially following surgery and is closely related to anxiety and depression. In **Chapter 7**, therefore, a specific feature of SEM (i.c. path modeling) is applied in order to unravel the potential pathways between these variables preoperatively and postoperatively. Consequently, possible tailored preoperative treatment that could affect postoperative fatigue is discussed.

The main findings of this thesis and interpretation of the results are discussed in **Chapter 8**. In addition, future perspectives on the improvement of quality of the convalescence period will be discussed.

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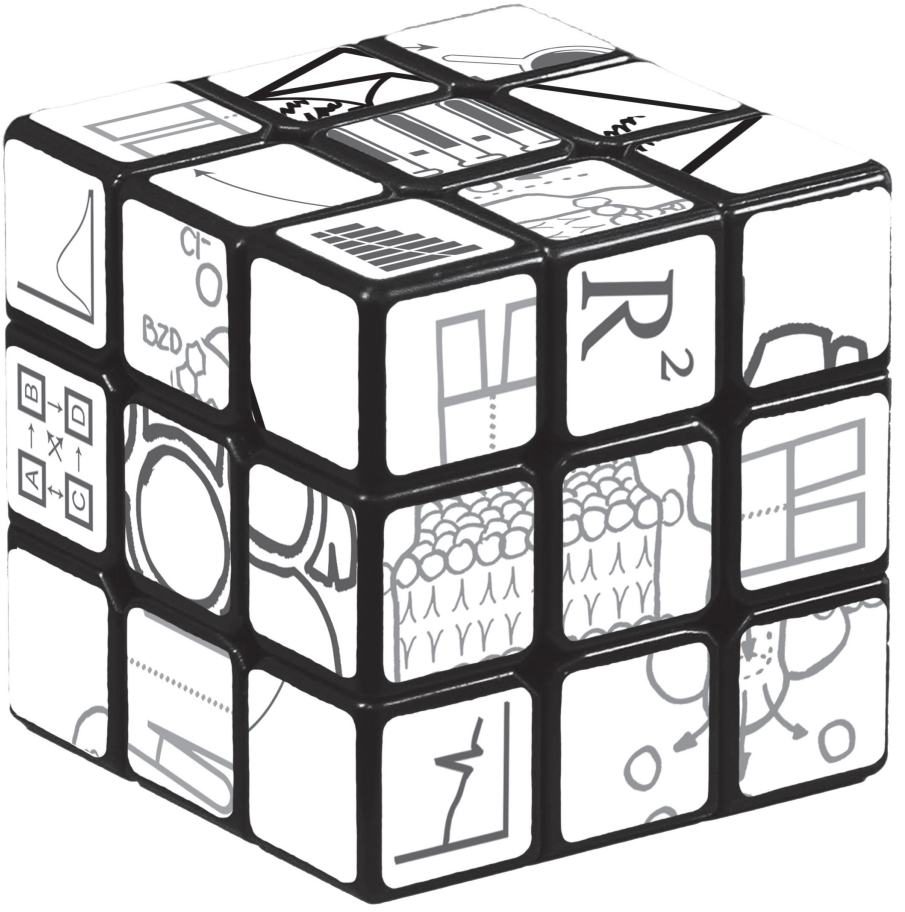
PREMEDICATION WITH LORAZEPAM AND OTHER BENZODIAZEPINES

PART 1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LORAZEPAM DOES NOT IMPROVE THE QUALITY OF RECOVERY IN DAY-CASE SURGERY PATIENTS: A RANDOMISED PLACEBO-CONTROLLED CLINICAL TRIAL

Herjan Mijderwijk
Stefan van Beek
Markus Klimek
Hugo J. Duivenvoorden
Frank Grüne
Robert Jan Stolker

CHAPTER 2

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ABSTRACT

In day-case surgery, the effects of the anxiolytic lorazepam as premedication on the quality of postoperative recovery are unknown. The objective was to evaluate whether lorazepam as a premedication beneficially affects quality of recovery (primary outcome) and psychological manifestations (secondary outcome) after day-case surgery. A randomised, double-blind, placebo-controlled clinical trial was executed in a single tertiary centre. Inclusion criteria included patients admitted for day-case surgery and age at least 18 years. Exclusion criteria were insufficient knowledge of the Dutch language; intellectual disability; ophthalmology surgery; extracorporeal shock wave lithotripsy; endoscopy; botulinum toxin A treatment; abortion; chronic pain treatment; preceding use of psychopharmaceuticals; contraindication to lorazepam. The intervention consisted of lorazepam (1 to 1.5 mg) intravenously vs. NaCl 0.9% as a premedication prior to surgery. The main outcome measure was the Quality of Recovery-40 (QoR-40) score. Secondary outcomes included State-Trait Anxiety Inventory (STAI-State/Trait); State-Trait Anger Scale (STAS-State/Trait); Multidimensional Fatigue Inventory (MFI); Hospital Anxiety and Depression Scale (HADS). Timing of evaluation: T0: preoperatively (all scales); T1: before discharge (STAI-State/Trait); T2: first postoperative working day (QoR-40); T3: 7th day after surgery (all scales). Robust regression analysis was applied. Statistical analyses were adjusted for the corresponding baseline value and sex. Four hundred patients were randomised; 398 patients were analysed. Postoperative mean QoR-40 scores were similar in both groups at T2 (174.5 vs. 176.4, $P = 0.34$) and T3 (172.8 vs.176.3, $P = 0.38$). Postoperative mean STAI-State/Trait scores decreased less in the group with lorazepam at T1 (32.3 vs. 29.3, $P < 0.0001$; 32.7 vs. 30.8, $P = 0.0002$). STAI-Trait and HADS-Anxiety decreased less in the group with lorazepam at T3 (31.1 vs. 30.0; $P = 0.03$, 3.3 vs. 2.5, $P = 0.003$). STAS-State increased in the group with lorazepam at T3 (10.8 vs. 10.3, $P = 0.04$). In day-case surgery, lorazepam as a premedication did not improve quality of recovery. Furthermore, this premedication may delay the decrease in postoperative anxiety and aggression.

TRIAL REGISTRATION ClinicalTrials.gov identifier: NCT01441843.

INTRODUCTION

The use of day-case surgery is increasing,[1,2] and even complex surgical procedures are now performed in a day-case setting.[3,4] Along with this increase, the psychological aspects of perioperative care have received greater attention in recent years.[5,6] Many patients have negative feelings about surgical procedures, a range of emotions covered by the term 'resistance'. The most prominent manifestation of resistance is anxiety, which in the preoperative period can affect the perioperative course. Induction of anaesthesia is more difficult in anxious patients,[7,8] and if the patient is anxious, more analgesics are needed postoperatively.[9] In addition, postoperative anxiety often follows preoperative anxiety, and patients are less satisfied with the perioperative experience.[9] Nevertheless, some healthcare professionals are reluctant to administer anxiolytic premedication because of concerns about delayed recovery.

A recent Cochrane review, however, concluded that because the use of anxiolytic premedication in day-case surgery does not negatively affect recovery duration; withholding anxiolytic premedication for that reason is not justified.[2] In addition, benzodiazepines for premedication in day-case surgery are reported to reduce anxiety preoperatively.[10]

In spite of these findings, whether benzodiazepines really improve the quality of postoperative recovery remains an unanswered question. For example, midazolam is the most prescribed premedication in day-case surgery; however, it has no beneficial effects on clinical recovery after surgery.[11] Lorazepam is less commonly used than midazolam but also serves as a premedication in day-case surgery.[12] Due to its greater anxiolytic effect and relatively long duration of action, lorazepam might be superior to midazolam in enhancing the quality of recovery. We hypothesised that a stronger anxiolytic drug with a prolonged effect such as lorazepam applied to a much larger study population might show more pronounced results in terms of improved quality of recovery.

The primary objective of this study, therefore, was to evaluate the effects of lorazepam on the quality of recovery in day-case surgery patients in a large-scale, randomised, parallel group trial. The secondary objective was to assess the effects of lorazepam on resistance in the postoperative period, including related manifestations of anxiety, aggression, feelings of fatigue and depressive mood.

METHODS

The study protocol was approved by the Medical Ethical Committee of Erasmus University Medical Centre, Rotterdam, The Netherlands (Chairperson Prof. dr. H.W. Tilanus) on 23 August, 2010, and by the Netherlands Central Committee on Research involving Human Subjects (CCMO) and registered with EudraCT number 2010-020332-19. The trial was also registered under identification number NCT01441843 in the ClinicalTrials.gov protocol registration system. Written informed consent was obtained from all participants.

Study population

Between October 2010 and September 2011, 400 patients were recruited from our day-case surgery department. Inclusion criteria were referral for day-case surgery and age at least 18 years. Patients were excluded if they exhibited clearly insufficient command of the Dutch language or intellectual disability, or were undergoing ophthalmology surgery, extracorporeal shock wave lithotripsy, endoscopy, botulinum toxin A treatment, abortion or chronic pain treatment. The latter procedures are generally considered as being minimally invasive, some cooperation of the patient is required and most practitioners are of the opinion that these do not require premedication. Additional exclusion criteria were the preceding use of psychopharmaceuticals and any contraindication to lorazepam use.

Study design

We conducted a randomised, parallel group design, with varying block sizes (8–10–12) across time. The ratio of allocation to either verum condition (lorazepam) or placebo condition (NaCl 0.9%) was 1 : 1. Randomisation was done by a computer-generated table, and patients were assigned subsequent numbers upon inclusion. Nurses who were not further involved in the care of these patients prepared the study medication according to the randomisation table. The study was double-blinded; the researchers, patients and all healthcare professionals involved in patient care were blinded to the treatment allocation.

Procedure and intervention

Figure 1 provides a timeline of the study procedure. All patients scheduled for day-case surgery received written information about the trial at least 1 week before surgery. A member of the research group enrolled patients after admission to the day-surgery centre. After giving written informed consent, patients completed a set of online

questionnaires while waiting for surgery (T0). Next, in the preoperative holding area, the independent recovery nurses, who had access to the group assignment document, prepared the medication. Blinding was achieved by preparation of the transparent fluids in identical syringes. Lorazepam was diluted in NaCl 0.9% to 4mg/4ml. Following our clinical routine depending on the patient's body weight (<75 and ≥75kg, respectively),

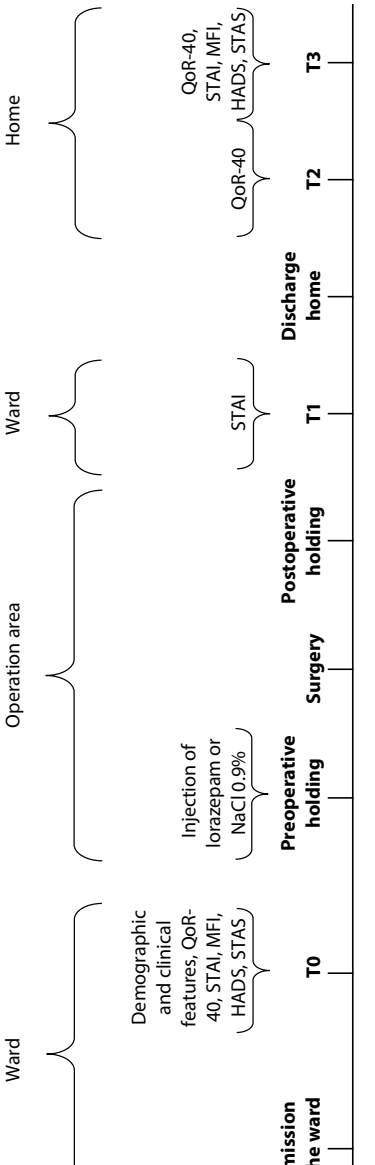

FIGURE 1 | Timeline of the study

T0: baseline assessment on the day of surgery (self-reported questionnaire); T1: assessment after surgery, before discharge (self-reported questionnaire); T2: first postoperative working day (administered by a healthcare professional); T3: seventh postoperative day (self-reported questionnaire); HADS, Hospital Anxiety and Depression Scale; MFI, Multidimensional Fatigue Inventory; QoR-40: Quality of Recovery Score-40; STAI, State-Trait Anxiety Inventory; STAS, State-Trait Anger Scale.

another nurse blinded to the treatment condition injected the single dosage of 1 or 1.5ml lorazepam/NaCl 0.9% by peripheral infusion 30 min before induction of anaesthesia. After the surgical procedure, patients completed another online questionnaire before discharge. On the first postoperative working day, a telephonic interview was done. On the sixth day after surgery, one of the researchers reminded the patients in a telephonic call to complete the last set of online questionnaires the next day (postoperative day 7).

Assessment of outcomes

Primary outcome

Quality of recovery after surgery was routinely assessed by a Dutch-translated version of the well validated 40-item Quality of Recovery Score-40 (QoR-40).[13,14] This questionnaire comprises five scales: physical comfort (12 items); emotional state (nine items); physical independence (five items); psychological support (seven items); and pain (seven items). Each item is rated on a five-point Likert scale, and the QoR-40 score is calculated as the sum of the scores on these scales. The higher is the score, the higher is the quality of recovery. QoR-40 has a good internal consistency, with Cronbach's α equal to 0.93.[14]

Secondary outcomes

Anxiety was measured using the Dutch version of the State-Trait Anxiety questionnaire (STAI).[15] The STAI consists of two 20-item scales; one measures how one generally feels (trait anxiety), and the other measures how one feels at the present moment (state anxiety). All items are rated on a four-point Likert scale. Scores for both scales are calculated by summing the scores on the items, and a higher score indicates a higher level of anxiety. STAI-State and STAI-Trait show similar internal consistencies (Cronbach's α >0.80, respectively[15]).

Fatigue was measured with the Dutch version of the Multidimensional Fatigue Inventory (MFI),[16] a 20-item questionnaire covering five scales (four items per scale): general fatigue; physical fatigue; mental fatigue; reduced motivation; and reduced activity. Each item is rated on a five-point Likert scale, and a higher score indicates a higher degree of fatigue. In general, MFI has a strong internal consistency, with Cronbach's α more than 0.80.[16]

Depressive moods were measured using a Dutch-translated version of the Hospital Anxiety and Depression Scale (HADS),[17] which consists of two seven-item scales, one for anxiety and one for depression. A higher score indicates a higher degree of depressive mood. For the Dutch general population, internal consistency (i.e. Cronbach's α) of

HADS equals 0.88.[18]

Aggression regulation was assessed with the Dutch-translated version of the State-Trait Anger Scale (STAS),[19] which consists of two 10-item scales, one covering the State aggression (how angry one feels at the moment) and one covering the Trait aggression (how angry one feels in general). Each item is rated on a four-point Likert scale, and a higher score indicates a higher degree of aggression. The internal consistency of STAS-State and STAS-Trait equals Cronbach's α of 0.93 and 0.88, respectively.[19]

The following demographic characteristics were assessed: sex; age; educational level; marital status; religion; and employment. At baseline, we also measured some clinical features: weight; height; heart rate; type of surgery; history of surgery; anaesthetic technique; and American Society of Anaesthesiologists (ASA) physical status classification.

Statistical analysis

To evaluate the possible beneficial effects of lorazepam, the following outcome variables were used: QoR-40 (five scales); STAI (both State and Trait scales); STAS (both State and Trait scales); MFI (five scales); and HADS (anxiety and depression scales). The expected clinical effect equals 0.50 in terms of standardised mean difference. For example, following Myles et al.,[14] the average score in the lorazepam and placebo conditions before surgery equals 183 (SD = 17). Then, we consider a positive difference of at least 8.5 in lorazepam compared with placebo to be clinically relevant. The nominal alpha is fixed at 0.05 (two sided). As the (scales of the) outcome variables were expected to be related, the number of independent scales (dimensions) of the outcome variables was estimated to be nine. Therefore, the real two-sided alpha had to be 0.05/9, whereas beta was fixed at 0.20. Consequently, a minimum number of 208 patients was required, 104 in each group. We expected that the percentage of dropouts would be 20%, meaning that the minimum number of patients required was 260, 130 in each group.

An intention-to-treat analysis was applied. Categorical data were tested with the Pearson chi-square test and continuous data with the Student's t-test for independent observations.

We applied robust regression analysis to test for differences in the primary and secondary outcome variables between the two groups. This approach can account for non-normal distribution of the outcome variables and also for heteroskedasticity.[20] In particular, we used MM estimation, which is a combination of least-trimmed squares estimator and

scale estimator, by which the variance of the estimator is minimised. To detect possible differences between verum and placebo on the outcome variables without bias, we adjusted for the baseline imbalance of the corresponding outcome variable and sex.

P-values (two-tailed) were estimated for all parameters. The regression analyses were done with SAS version 9.2 (SAS Institute Inc, Cary, NC, USA);[21] all other analyses were performed with SPSS software version 17.0 (SPSS Institute, Chicago, IL, USA).

RESULTS

Study population

A total of 3820 patients were assessed for eligibility; 3420 were excluded and consequently, 400 patients were randomised to either lorazepam or NaCl 0.9%.
Twelve patients in the lorazepam group and six in the NaCl 0.9% group were lost to follow-up for at least one of the measurement periods. For detailed information, see Figure 2.

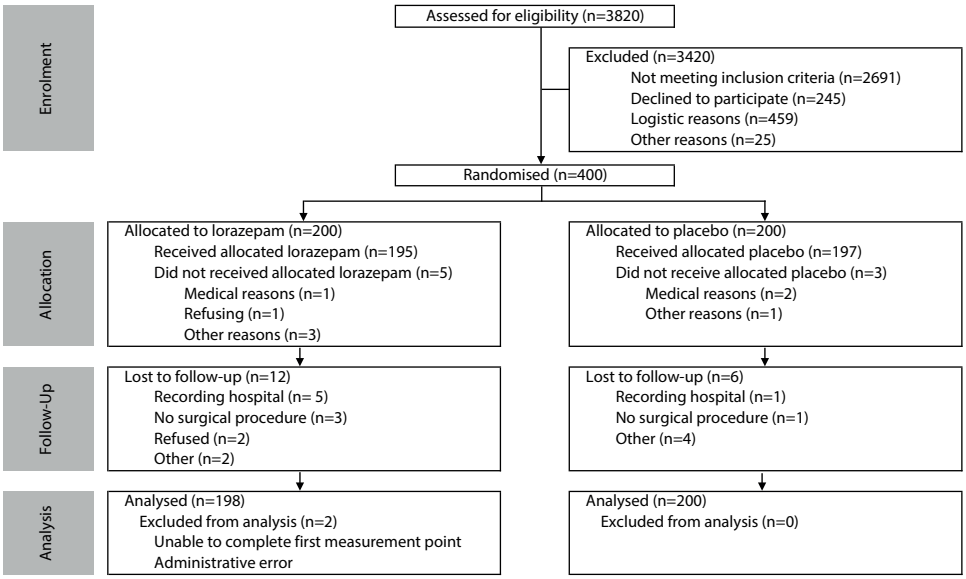

FIGURE 2 | A flowchart showing patient flow according to the study protocol

In retrospect, two patients in the lorazepam group should not have been included; one could not complete the baseline measurements for technical reasons and the other admitted afterwards to using psychoactive drugs. Data for these two patients were, therefore, excluded from analysis. In total, 14 patients from the lorazepam group and six patients from the NaCl 0.9% group were lost to follow-up for at least one of the measurement points. This difference was not significant ($P = 0.11$, two tailed).

General characteristics

Overall, general patient characteristics did not significantly differ between the two groups (Table 1).

Primary outcome

Table 2 shows the mean QoR-40 scores for both groups at T0, T2 and T3. In both groups, the mean scores were high at all time points. Regarding the lorazepam group, mean values were 177.2 at T0, 174.5 at T2 and 172.8 at T3. With respect to the NaCl 0.9% group, mean values were 180.4 at T0, 176.4 at T2 and 176.3 at T3. Although the mean scores slightly decreased after surgery, the differences between the groups were not significant after adjustment for the baseline QoR-40 score and sex at T2 ($X^2 = 0.93$; $P = 0.34$) or at T3 ($X^2 = 0.77$; $P = 0.38$). Lorazepam showed no statistically significant effect on the quality of recovery after surgery.

Secondary outcomes

Anxiety measured at T1 was statistically significantly higher in the lorazepam group. The two groups also differed on STAI-State ($X^2 = 18.50$; $P < 0.0001$) and STAI-Trait ($X^2 = 14.26$; $P = 0.0002$), with the effect that the postoperative decrease in anxiety was smallest in the lorazepam group (Table 3). The decrease in STAI-State scores was greater in the placebo group (from 37.6 to 29.3 at T1) than in the lorazepam group (from 38.6 to 32.3 at T1). STAI-Trait scores in the placebo group also dropped significantly more (from 33.4 to 30.8 at T1) than in the lorazepam group (from 33.6 to 32.7 at T1).

The two groups differed significantly on three outcome variables (Table 4): STAI-Trait ($X^2 = 5.27$; $P = 0.03$); HADS-Anxiety ($X^2 = 9.26$; $P = 0.003$); and STAS-State ($X^2 = 4.45$; $P = 0.04$) at T3. The postoperative decrease in STAI-Trait scores was greater in the placebo group (from 33.4 to 30.0 at T3) than in the lorazepam group (from 33.6 to 31.1 at T3). HADS-Anxiety scores in the placebo group also dropped significantly more (from 4.7 to 2.5 at T3) than in the lorazepam group (from 4.6 to 3.3 at T3). STAS-State scores slightly (but significantly) increased more in the lorazepam group (from 10.1 at T0 to 10.8 at T3) than in the placebo group from (10.3 at T0 to 10.3 at T3).

TABLE 1 | Patient characteristics at baseline

	Intervention		
	Lorazepam, n=198 (%)	NaCl 0.9%, n=200 (%)	*P*[*]
Demographic			
Sex			0.63
Female	89 (44.9)	85 (42.5)	
Male	109 (55.1)	115 (57.5)	
Age (mean; SD)	39.5; 13.7	39.3; 13.6	0.88
Educational level[a]			0.12
Low	26 (13.1)	37 (18.5)	
Mid-level	144 (72.7)	126 (63.0)	
High	28 (14.1)	37 (18.5)	
Marital status[b]			0.94
Single	79 (39.9)	79 (39.5)	
Together	119 (60.1)	121 (60.5)	
Religion			0.23
Yes	58 (29.3)	70 (35.0)	
No	140 (70.7)	130 (65.0)	
Employment			0.77
Yes	151 (76.3)	150 (75.0)	
No	47 (23.7)	50 (25.0)	
Clinical			
Weight (mean; SD)[c]	78.8; 15.6	79.6; 15.2	0.64
Height (mean; SD)[d]	176.5; 10.1	176.9; 10.1	0.68
Heart rate (mean; SD)[e]	69.9; 12.8	70.9; 13.5	0.44

TABLE 1 | Patient characteristics at baseline *(continued)*

	Intervention		
	Lorazepam, n=198 (%)	NaCl 0.9%, n=200 (%)	*P**
Type of surgery			0.51
General	60 (30.3)	44 (22.0)	
Otorhinolaryngologic	8 (4.0)	12 (6.0)	
Gynaecologic	25 (12.6)	32 (16.0)	
Urologic	20 (10.1)	26 (13.0)	
Orthopedic	46 (23.2)	46 (23.0)	
Plastic	31 (15.7)	34 (17.0)	
Dental/faciomaxillary	8 (4.0)	6 (3.0)	
Had surgery before			0.28
Yes	159 (80.3)	169 (84.5)	
No	39 (19.7)	31 (15.5)	
Anaesthesia technique[f]			0.09
General	167 (85.2)	182 (91.5)	
Peripheral regional	14 (7.1)	11 (5.5)	
Neuraxial	15 (7.7)	6 (3.0)	
ASA[g]			0.32
ASA I	133 (67.2)	125 (62.5)	
ASA II	62 (31.3)	74 (37.0)	
ASA III	3 (1.5)	1 (0.5)	

*)*P*-values are rounded upwards; [a)]Low: no education, elementary school, preparatory middle-level vocational education; Mid-level: middle-level vocational education, higher general continued education, higher vocational education; High: preparatory university education, university education; [b)]Single: unmarried, divorced, widow(er); Together: married, living together; [c)]Weight: body weight in kilograms; [d)]Height: body length in centimeters; [e)]Heart rate: beats per minute, n verum=197 and n placebo=199 due to cancelling surgical procedure; [f)]n verum=196 and n placebo=199 due to cancelling surgical procedure; [g)]risk classification according to the American Society of Anesthesiology.

TABLE 2 | Changes in primary outcome (QoR-40)[*] over one week

	Lorazepam	NaCl 0.9%		95% CIs			
	Mean (SD) [n]	Mean (SD) [n]	Mean (diff)[$]	lower	upper	χ^2	$P^{\#}$
Baseline assessment (T0)	177.2 (17.4) [198]	180.4 (17.5) [200]	NA	NA	NA	NA	NA
First working day after surgery (T2)	174.5 (13.0) [191]	176.4 (12.6) [197]	1.1	-3.5	1.2	0.93	0.34
Seventh postoperative day (T3)	172.8 (21.0) [188]	176.3 (18.8) [195]	-0.4	-5.0	1.9	0.77	0.38

CIs=Confidence Interval; [*]Min–max score: 40–200; [#]*P* values are rounded upwards. Tested by robust regression analysis (adjusted for baseline and sex), using MM estimation; [$]condition coded as 0 (placebo) and 1 (lorazepam). QoR-40, Quality of Recovery Score-40.

TABLE 3 | Changes in secondary outcome variables on treatment day

	Lorazepam		NaCl 0.9%						
	T0	T1	T0	T1					
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)		95% CIs			
	n=198	n=191	n=200	n=197	Mean (diff)[$]	lower	upper	χ^2	$P^{\#}$
Anxiety									
STAI-State	38.6 (8.8)	32.3 (7.5)	37.6 (10.0)	29.3 (6.7)	2.1	1.5	4.0	18.50	<0.0001
STAI-Trait	33.6 (8.2)	32.7 (8.3)	33.4 (7.9)	30.8 (7.1)	1.8	0.8	2.4	14.26	0.0002

CIs=Confidence Interval; [#]*P*-values are rounded upwards. Tested by robust regression analysis (adjusted for baseline and sex), using MM estimation; [$]condition coded as 0 (placebo) and 1 (lorazepam); T0=baseline; T1=after surgery, before discharge. STAI, State-Trait Anxiety Inventory.

TABLE 4 | Changes in secondary outcome variables over one week

		Lorazepam		NaCl 0.9%						
		T0	T3	T0	T3					
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)		95% CIs			
	Score (min–max)	n=198	n=188	n=200	n=195	Mean (diff)[5]	lower	upper	χ^2	*P*[#]
Anxiety										
STAI-State	20–80	38.6 (8.8)	31.4 (9.7)	37.6 (10.0)	29.4 (7.9)	1.1	-0.3	2.6	2.43	0.12
STAI-Trait	20–80	33.6 (8.2)	31.1 (9.4)	33.4 (7.9)	30.0 (8.0)	0.7	0.2	2.0	5.27	0.03
HADS	0–21	4.6 (3.3)	3.3 (3.2)	4.7 (2.9)	2.5 (2.7)	0.7	0.2	1.0	9.26	0.003
Fatigue										
MFI	20–100	43.1 (13.7)	51.1 (17.7)	40.1 (12.3)	46.0 (15.9)	1.9	-0.5	4.8	2.61	0.11
Aggression										
STAS-State	10–40	10.1 (0.8)	10.8 (3.3)	10.3 (1.5)	10.3 (1.2)	0.6	0.0	1.0	4.45	0.04
STAS-Trait	10–40	13.8 (3.8)	13.4 (4.0)	13.1 (3.3)	12.9 (3.2)	-0.1	-0.2	0.6	1.02	0.32
Depression										
HADS	0–21	3.1 (2.4)	3.1 (3.3)	3.0 (2.4)	2.5 (2.5)	0.4	-0.2	0.6	1.07	0.31

CIs=Confidence Interval; [#]*P*-values are rounded upwards. Tested by robust regression analysis (adjusted for baseline and sex), using MM estimation; [5]condition coded as 0 (placebo) and 1 (lorazepam); T0=baseline; T3=seventh postoperative day. HADS, Hospital Anxiety and Depression Scale; MFI, Multidimensional Fatigue Inventory; STAI, State-Trait Anxiety Inventory; STAS, State-Trait Anger Scale.

DISCUSSION

This study is the first randomised controlled trial with a strong methodological framework to address the effects of intravenous premedication with lorazepam on the quality of recovery. The principal finding is the lack of any beneficial effect of premedication with lorazepam on the quality of recovery in the day-case surgery setting. In addition, we found that the postoperative decrease in anxiety was lower in the lorazepam group and that aggression scores had increased in this group, both to a statistically significant level. Our results support the reluctance of some healthcare professionals to routinely administer anxiolytic premedication in day-case surgery.[22]

We chose lorazepam for its proven anxiolytic properties.[23] Furthermore, it has been used as a reference anxiolytic medication.[24] Schunck et al.[25] recently showed that a single intravenous dosage (as we used) reduced anxiety for patients at a moderate level, although it was not strong enough to suppress a panic attack. The more commonly used midazolam has unpredictable effects and a relatively high risk of paradoxical reactions, although this risk is much lower with lorazepam.[26] Moreover, Kain et al.[11] showed that despite a reduction in anxiety, midazolam did not improve clinical recovery in day-case surgery. According to their study, we expected that an alternative anxiolytic administered on a different schedule in relation to surgery might result in different findings.

We found that even lorazepam, which is considered the most potent anxiolytic benzodiazepine, had no beneficial effects on the quality of recovery or on the manifestations of resistance. This may be due to the low preoperative anxiety levels, as the effects of lorazepam could differ depending on the perceived level of threat.[24] In our population, baseline scores of anxiety were not high, fitting with our high score of quality of recovery, which is in line with the literature in patients undergoing minor/day-case surgery.[27,28]

Our second finding was a minor, unwanted, adverse reaction to lorazepam. The lower decrease in anxiety and increase in aggression in the lorazepam group was statistically significant because of our large sample size; however, this might also be clinically relevant, as administration of a drug with a risk of side effects and without a proven beneficial effect should be avoided.

A rebound effect after lorazepam use might be a possible explanation for our findings. The rebound phenomenon is well described with benzodiazepine use; it may occur when the treatment is stopped after a certain (longer) time period.[29,30] Kales et al.,[31,32]

however, also found a rebound effect after low dosages of benzodiazepines. The molecular mechanisms behind the rebound phenomenon following acute treatment are not yet completely understood.[33] As Huopaniemi et al.[33] showed that a single dosage of a benzodiazepine can change genetic transcription processes, our findings in this study might fit with the idea of a rebound effect even after the administration of a single dosage of lorazepam.

Although a rebound phenomenon points to a (too) short action of the drug, a more obvious explanation might simply lie in the fact that patients with a low preoperative anxiety score might experience a prolonged decrease in their level of awareness secondary to lorazepam as an unwanted side effect. The day-case setting relies on the 'patient in control', and the prolonged effects of lorazepam might be disadvantageous in that setting. The relatively long half-life of lorazepam supports this explanation. It is unclear whether this phenomenon is present after the administration of benzodiazepines with a shorter duration of action.

Due to the lack of a positive postoperative effect (in addition to these negative effects), together with the results from Kain et al.[11] and the potential risk of delirium,[34,35] we cannot support the routine administration of benzodiazepines as a premedication in perioperative care.

It is worthwhile mentioning that we found significant differences regarding STAI-Trait throughout the follow-up period. This was unexpected, as STAI-Trait measures how one feels in general, and, therefore, should be stable in the follow-up period. However, literature shows that STAI-Trait does not only measure trait anxiety but also assesses negative affect.[36] Therefore, the changes on STAI-Trait might be interpreted as the reflection of negative feelings, rather than trait anxiety. These findings have lead to the proposal of a revision of the questionnaire.[36] The version we used in our study, however, is validated, but we are aware of these concerns.

Our findings should be interpreted in the context of our study methodology and its limitations. Ideally, lorazepam administration should be exactly weight dependent; however, the dosages used in the current work are standard dosages in our daily clinical routine. Higher dosages are believed to provoke unwanted side effects such as respiratory depression, drowsiness and amnesia and are, therefore, not indicated for patients in day-case surgery, and might also have led to an unblinding of the study.

Premedication for surgical patients is normally given per os. The pharmacokinetics

of oral lorazepam show a broad variation with a maximum effect at around 2h after administration,[37] and we wanted to avoid the influence of circadian rhythm on drug absorption.[38] Furthermore, in clinical practice, especially in a day-case surgery setting, oral administration of premedication is not always in time for all patients. Overall, the timing of drug administration and the measuring time points in our study reflect common practice in research performed in day-case surgery.[11,29,39,40] The time to onset of effect after intravenous injection of lorazepam is less than 5 min.[41]

The study design might also have been more streamlined with a consistent anaesthetic technique, but some patients had neuraxial or peripheral regional anaesthesia rather than general anaesthesia. Nevertheless, this study reflects daily clinical practice, and because of our randomised design, there is no reason to think that possible unmeasured confounders differed between the two conditions.

We excluded 459 patients for logistical reasons, due to the interval between eligibility assessment and the beginning of the surgical procedure being too short. A much smaller group of patients (245) refused to participate. We were unable to detect any selection bias.

In our opinion, this study should be repeated in hospitalised patients undergoing major surgery who may be facing a longer stay in the hospital, resulting in higher preoperative anxiety levels, and probably more pronounced effect sizes regarding fatigue and depression. Such a study could well yield findings that differ from ours, particularly when ethnic and sociocultural aspects are taken into account. In addition, we have described the effects of lorazepam for a whole study population. We believe, however, that it might be possible to identify subgroups of patients who could benefit from premedication. Future studies should be tailored to identifying these vulnerable patients.

CONCLUSION

In this randomised controlled trial, with a strong methodological framework, we addressed the effects of routine intravenous premedication with lorazepam on the quality of recovery in the day-case surgery setting. We found no improvement in the quality of recovery in adult day-case surgery patients, but observed that the use of lorazepam as a premedication may delay the decrease in postoperative anxiety and aggression. The routine use of lorazepam for premedication in adult day-case surgery patients should, therefore, be questioned. Further research is needed to establish

whether these findings can be generalised to other benzodiazepines and/or other patient groups.

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IMPLICATION OF *UGT2B15* GENOTYPE POLYMORPHISM ON POSTOPERATIVE ANXIETY LEVELS IN PATIENTS RECEIVING LORAZEPAM PREMEDICATION

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CHAPTER 3

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ABSTRACT

Lorazepam is used as premedication for its anxiolytic properties. The *UGT2B15* genotype is of importance for the metabolism of lorazepam. The clinical effect of genetic polymorphisms in *UGT2B15* genotype on the treatment of anxiety levels in same-day surgery patients receiving lorazepam, however, is unknown. Three hundred ninety-eight same-day surgery patients of mixed sex (from a previous double-blinded randomized controlled trial who were assigned to either lorazepam [n = 198] or placebo [n = 200]) were assessed for the *UGT2B15*2* variant allele. Anxiety was measured preoperatively and postoperatively by the State part of the State-Trait Anxiety Inventory. The difference between these 2 measurements served as outcome of the study. Analysis of variance was used to assess the State part of the State-Trait Anxiety Inventory difference for interactions among the following factors: *UGT2B15* genotype status, treatment condition (lorazepam or placebo), patient sex, and preoperative anxiety score. The anxiety difference was complex in that the interaction of lorazepam and *UGT2B15* genotype status also was dependent on the joint effect of patient sex and preoperative anxiety score ($F = 7.15$, $P = .008$). Further exploration showed clinical relevant results in patients with high preoperative anxiety scores. Striking was that females with high preoperative anxiety scores and genetically reduced lorazepam glucuronidation (*UGT2B15*2* homozygotes) showed more postoperative anxiety reduction than males with the same genotype. *UGT2B15* genotype contributes to postoperative anxiety reduction after lorazepam premedication. Future research that focuses on patients with high preoperative anxiety scores could help to gain a deeper understanding in the clinical relevance of the interaction between lorazepam and *UGT2B15* genotype on postoperative anxiety levels.

INTRODUCTION

Uridine 5′-diphosphate-glucuronosyltransferases (UGTs) are phase II enzymes that have a prominent role in biotransformation of endogenous and exogenous substrates.[1] UGTs primarily facilitate glucuronidation. Glucuronidation is the process in which glucuronic acid is linked to a substrate by means of a catalyzing UGT enzyme.[2] Consequently, the substrate can be eliminated.[2] UGTs generally are grouped into the UGT1 and UGT2 families.[3] *UGT2B15* is one of the UGT enzymes. The major drug substrate for *UGT2B15* is lorazepam.[2] Lorazepam clearance is executed primarily by direct glucuronidation followed by mainly renal excreation.[4]

It is known that the *UGT2B15* genotype has a strong influence on the pharmacokinetics of lorazepam: 61% of the total variance in lorazepam clearance is explained by this *UGT2B15* genotype in healthy subjects.[5] Lévesque et al.[6] showed that a guanine-to-thymine change in *UGT2B15* genotype leads to an amino acid substitution at position 85 from aspartic acid (D) to tyrosine (Y), resulting in the *UGT2B15($D^{85}Y$)* genetic polymorphism (ie, *UGT2B15*2)*. As a consequence, homozygous subjects have reduced glucuronidation compared with wild-type and heterozygous carriers. Therefore, homozygous subjects have been shown to have significantly greater lorazepam concentrations.[5] Without a change in the general pharmacodynamics (which is the S-shaped dosage-effect relationship) of lorazepam, these greater plasma levels will induce more pronounced clinical effects in patients with *UGT2B15*2* polymorphism.

Clinical effects of lorazepam (sedation, psychomotor performance, alertness, motor function and coordination) show a large variability in humans according to the *UGT2B15* genotype.[5] However, the effect of lorazepam on anxiety according to genotype is of clinical importance—as it is widely used for its anxiolytic properties,[7] such as anxiolytic premedication[8]—but it is still unknown.

If the anxiolytic effect of lorazepam differs significantly according to the *UGT2B15* genotype, this may in part explain patient variability in anxiolytic effect. Therefore, we evaluated interactions between lorazepam and *UGT2B15* genotype. In addition, we assessed interactions with patient sex and preoperative anxiety score because these determinants are relevant in studies with lorazepam and perioperative patient anxiety.[9,10]

METHODS

This study is a derivative of a larger completed randomized controlled clinical trial (RCT) conducted and completed at the Erasmus University Medical Center with the same study population, study design, procedure and assessments of outcomes. Therefore these sections of the methods in this study are in line with our previous publication.[9] The primary and secondary objectives of the original RCT were to evaluate the effects of lorazepam (versus placebo) on the quality of recovery and psychological phenomena, including anxiety, in same-day surgery respectively.[9] The RCT showed that, among others, lorazepam did not improve quality of recovery and that the expected decrease in postoperative anxiety was lower in the lorazepam group.[9]

This study protocol was approved by the Medical Ethical Committee of Erasmus MC and by the Netherlands Central Committee on Research involving Human Subjects (CCMO) and registered with EudraCT number 2010-020332-19. The trial is also registered under identification number NCT01441843 in the ClinicalTrials.gov protocol registration system. Signed written informed consent was obtained from all patients including whether they consented to genotyping (see also Table 1).

Study population

Between October 2010 and September 2011, 400 patients were recruited from our same-day surgery department.[9] Inclusion criteria were as follows: all patients who were referred for same-day surgery and at least 18 years of age. Patients were excluded if they met one or more of the following criteria: clearly insufficient command of the Dutch language, mental retardation, undergoing eye surgery, extracorporeal shock wave lithotripsy (ESWL), endoscopy, Botox treatment, abortion, or chronic pain treatment. The latter procedures are generally considered as low invasive, some cooperation of the patient is required, and most practitioners agree that these do not require premedication. Finally, preceding use of psychopharmaceuticals and contraindication to lorazepam use were exclusion criteria as well.

Study design

This study was a randomized, double blinded, placebo-controlled clinical trial with a parallel group design, with varying block sizes (8-10-12) across time. The ratio of allocation to the treatment conditions (lorazepam or placebo) was 1:1. Randomization was performed by a computer-generated table, and the patients were assigned subsequent numbers on inclusion. Health care professionals, patients, and researchers were blinded to the treatment condition; however nurses

who were not involved directly in the care of these patients, prepared the study medication according to the randomization table. A flowchart from this study has been published.[9]

Procedure

Figure 1 provides a timeline of the study procedure. All patients scheduled for same-day surgery received written information about the trial at least 1 week before surgery. A member of the research group enrolled patients after admission to the day-surgery center and sought written informed consent. Patients who consented to participate completed a set of online questionnaires when waiting for surgery (T0). Next, in the preoperative holding, the independent recovery nurses, who had access to the group assignment document, prepared the medication. Blinding was achieved by preparing the transparent fluids in identical syringes. Depending on the patient's body weight, respectively < 75kg and ≥ 75kg, another nurse blinded to treatment condition injected the single dosage of 1mg or 1.5mg lorazepam by peripheral infusion 30 minutes before induction of anesthesia. The placebo group received an equal volume of NaCl 0.9%. The recovery nurses obtained 8ml venous blood from the peripheral infusion. After the surgical procedure, patients completed an online questionnaire before discharge (T1). Because of the long duration of action with known therapeutic concentrations even after a single intravenous dosage,[11] the preoperative injected lorazepam was considered to be active at the moment of postoperative anxiety testing.

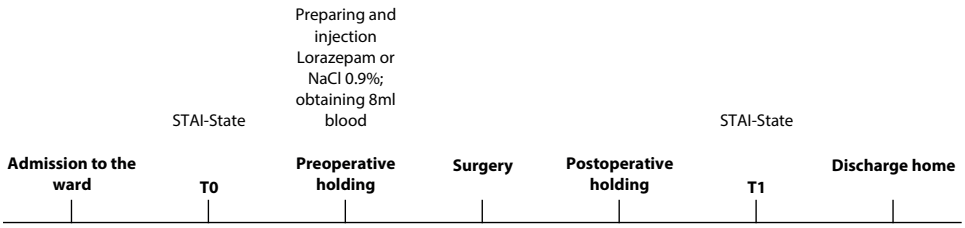

FIGURE 1 | Timeline of the study

STAI-State, State-Trait Anxiety Inventory, State part; T0 = preoperative assessment; T1 = postoperative assessment.

Genotype determination

UGT2B15 genotyping was done using the Taqman allelic discrimination assay on an ABI PRISM 7500 FAST sequence detection system. The assay consisted of a master mix (TaqMan® GTXpress™ Master Mix, Applied Biosystems, Nieuwerkerk a/d IJssel, the Netherlands) and two-specific minor groove binding (MGB) probes, labelled with the fluorescent dyes VIC and FAM. For the *UGT2B15*2* (253G>T) variant, we used a commercial available Drug Metabolizing Enzyme (DME) assay mix: C__27028164, rs1902023 (Applied Biosystems). Each reaction was performed in a 10 µL reaction mix containing 2 µL of DNA template (10ng/ µL). The thermal profile consisted of an initial pre-read step at 60°C for 1 minute, denaturation at 95°C for 20 seconds, followed by 45 cycles of denaturation at 92°C for 3 seconds, and an annealing and extension step at 60°C for 30 seconds, followed by a post-read step at 60°C for 1 minute. Genotypes were scored by measuring allelic-specific fluorescence using the 7500 software version 2.0.5 for Allelic Discrimination (Applied Biosystems).

Outcome

Anxiety was measured by the Dutch version of the State-Trait Anxiety questionnaire (STAI).[12] STAI consists of two scales, each containing 20 items. We used the State scale (STAI-State) in this study because this scale measures how the patient feels at the moment of completing the questionnaire.[12] Conversely, the Trait scale measures how one generally feels.[12] Theoretically, the latter is not expected to be affected by a stressful situation like surgery. We calculated the sum score by summing the scores on the items, theoretically ranging from 20 to 80. Greater scores indicate a higher level of anxiety. In this study, differences in STAI-State levels relative to the preoperative score served as outcome. Thus, anxiety difference was calculated by subtracting the postoperative anxiety score from the preoperative anxiety score. Consequently, a positive difference indicates that the postoperative anxiety score is lower than the preoperative anxiety scores, and a negative difference indicates an increase in anxiety in the postoperative period. The median score of these anxiety differences are called 'median differences' in this work.

Determinants

We used a recessive genetic model for analyzing *UGT2B15* genotype because previous literature suggests pharmacodynamic differences according to such a model.[13] This means that only patients who were homozygous for the *UGT2B15*2* variant were scored as deviant *UGT2B15* genotype. As a result, wild type *UGT2B15* and heterozygous *UGT2B15*2* were scored as normal *UGT2B15* genotype. In addition, treatment condition

(lorazepam or placebo), patient sex, preoperative anxiety score were also used as a determinants.

Statistical analysis

Four-way analysis of variance was used to assess anxiety scores for interaction between the following factors: *UGT2B15* genotype status, treatment condition, patient sex and preoperative anxiety score. The effects were evaluated by F-tests and the corresponding *P* values. The model was adjusted for type of surgery (ie, surgical speciality) and type of anesthesia (ie, general anesthesia, peripheral regional, and neuraxial). The distribution of the constructed outcome (ie, anxiety difference) was considered normal according to the obtained histogram and Q-Q plot. The Kolmogorov-Smirnov test and Shapiro-Wilk test turned out to be statistical significant nonetheless. Neither the square root transformation nor the log transformation was adequate to achieve a normal distribution for the anxiety score including the residuals. Therefore, analysis of variance was still performed because this method has been shown to be resilient for nonnormality.[14-17] It was checked whether there were influential observations (standardized residuals ≥ ±3.0). There was 1 influential observation. The equality of error variances was evaluated by the Levene's test, which was non-significant ($P = .34$). The percentage of variance explained by the model was based on the coefficient of determination (R^2).

To get a full understanding of the anxiety difference, we analyzed the effect of *UGT2B15* genotype in combination with treatment condition, patient sex and preoperative anxiety score. Therefore, we had to test for higher order interactions. Significant statistical interaction implies that the used variables act dependently on the outcome variable.[18] All possible interactions with either *UGT2B15* genotype or treatment condition were tested simultaneously for significance and all main terms. Interaction between variables means that the effect of variable x_1 is modified by the value of variable x_2, and x_3, etc. When a higher-order interaction appeared to be statistical significant, the outcome is explained by the combination of multiple variables. Consequently, possible significant effects of lower order interactions are less relevant if a higher order interaction turned out to be significant.[19] Therefore, we only presented and described the results of the statistically significant highest order interaction for STAI-State.

All statistical testing took place at .05 level of statistical significance (two-sided). All analyses were done with SPSS software 20.0 (IBM Corp. Armonk, NY).

RESULTS

Patients

In the original study, 400 eligible patients were randomized to either lorazepam or placebo. Three hundred ninety-eight patients were analyzed.[9] The number of missing values on the outcome variable did not appear to be significantly different between the lorazepam or placebo group (Fisher's exact test 0.22). Furthermore, the number of missing values of *UGT2B15* genotype did not differ between these 2 groups (Fisher's exact test 0.84).

The study population included 224 males (56%) and had a mean age of 39.4 years (standard deviation, 13.6). The groups made by randomization have an equally distributed number of patients. For *UGT2B15*2* polymorphism, 185 patients (50%) were heterozygous and 102 patients (27%) were homozygous deviant. The wild type group comprised 85 patients (23%). These frequencies are consistent with Hardy-Weinberg equilibrium (P = .95, Pearson X^2 square). Overall, the level of anxiety was reduced postoperatively (Table 1 and Table 2).

All main terms together with all possible interactions including *UGT2B15* genotype and treatment condition are presented in Table 3. The highest order interaction that was statistically significant comprised the following variables: *UGT2B15* genotype, treatment condition, patient sex, and preoperative anxiety score ($F = 7.15$; $df = 1, 339$; $P = .008$).

Interpretation of higher order interactions can be complex.[19] For a more detailed understanding of this interaction and its clinical meaning and significance, the median differences and other descriptive statistics of patient categories on STAI-State according to the used determinants are presented and visualized in Appendix 1 and Figure 2, respectively. Because the preoperative measurement of STAI-State is continuous, we dichotomized the scores at the overall mean level of STAI-State to make visualization feasible. Anyway, this did not affect the results.

According to STAI-State descriptive statistics (Appendix 1), median differences range from -0.50 to 18.00. As mentioned previously, positive median differences represent a decrease of anxiety postoperatively.

Patients with low preoperative anxiety scores

Median differences of patients with low preoperative anxiety scores showed a range from -0.50 to 7.00. All female groups together with males in the placebo condition

TABLE 1 | Descriptive analysis of used variables

	n	%	
Sex			
Male	224	56.3	
Female	174	43.7	
Treatment condition			
Lorazepam	198	49.7	
Placebo	200	50.3	
UGT2B15 Genotype Polymorphism			
Wild type	85	22.8	
Heterozygous	185	49.7	
Homozygous	102	27.4	
	Median	IQR, percentiles	
		25	75
Anxiety (STAI-State)			
Preoperative (*n*=398)	37.0	31.75	44.00
Postoperative (*n*=388)	30.0	26.00	35.00

n= number of patients; % = percentage; IQR = interquartile range; STAI-State = State-Trait Anxiety Inventory, State part; Minimum-maximum score STAI-State = 20-80.

TABLE 2 | Pre- and postoperative anxiety scores

	Preoperative median STAI-score		Postoperative median STAI-score	
	UGT2B15 wt/ht	*UGT2B15* hz	*UGT2B15* wt/ht	*UGT2B15* hz
Lorazepam	36.00	39.00	32.00	30.00
Placebo	36.00	35.00	29.00	27.50

STAI-State = State-Trait Anxiety Inventory, State part; *UGT2B15* wt/ht = wild type and heterozygous *UGT2B15*2*; *UGT2B15* hz = homozygous *UGT2B15*2*.

TABLE 3 | Significance testing of anxiety difference

Source of variation	F-test †	*P* value
UGT2B15 (U)	0.06	.80
Treatment Condition (C)	1.09	.30
Sex (S)	2.11	.15
Preoperative Anxiety Score (P)	225.29	<.0001
U*C*S	8.00	.005
U*C*P	0.71	.40
U*C*S*P	7.15	.008

† Corresponding degrees of freedom 1, 339; * = interaction; STAI-State = State-Trait Anxiety Inventory, State part; Sex was coded as 1 for females and 0 for males. Treatment condition was coded as 1 for lorazepam and 0 for placebo. *UGT2B15* was coded as 1 for homozygous *UGT2B15*2* and 0 for wild type *UGT2B15* and heterozygous *UGT2B15*2*. Analysis adjusted for surgical speciality and type of anesthesia. Model R Squared = 0.72 (Adjusted R Squared = 0.70).

showed anxiety reduction in the postoperative period independently of *UGT2B15* genotype. This was not observed for males in the lorazepam condition: males with normal *UGT2B15* genotype showed no anxiety reduction, whereas males with deviant *UGT2B15* genotype did show anxiety reduction (Figure 2).

Patients with high preoperative anxiety scores

Median differences of patients with high preoperative anxiety scores showed a range from 9.00 to 18.00. Thus, all patient categories showed anxiety reduction in the postoperative period. Males in the lorazepam condition with normal *UGT2B15* genotype showed greater anxiety reduction than males with deviant *UGT2B15* genotype. In contrast, females in the lorazepam condition showed opposite results (Figure 2, Appendix 1).

Males in the placebo condition with normal *UGT2B15* genotype showed less anxiety reduction than males with deviant *UGT2B15* genotype. In contrast, females in the placebo condition showed opposite results (Figure 2, Appendix 1).

DISCUSSION

The principal finding of this study is that the *UGT2B15* genotype has an influence on postoperative anxiety levels in same-day surgery patients receiving a single dosage of lorazepam as premedication. This clinical effect also depends on patient sex and preoperative anxiety score. Our finding supports data from previous research showing a large variability in clinical effects of lorazepam in healthy volunteers.[5]
For the anxiety median differences, most clinical significant results were seen in patients

with high preoperative anxiety scores (Figure 2). They showed more reduction in anxiety compared with patients with low preoperative anxiety scores. Therefore, we believe that the significant highest-order interaction is predominately driven by patients with high preoperative anxiety scores. In light of clinical significance (i.e. median differences ≥9.0 on a 20 – 80 point scale),[20] we discuss these patient categories only.

The figures show that anxiety reduction in patients treated with placebo is likely because of the well-known placebo effect, because pharmacologic interaction between placebo and *UGT2B15* genotype is not known. Preoperative administration of placebo is known to reduce postoperative anxiety.[9]

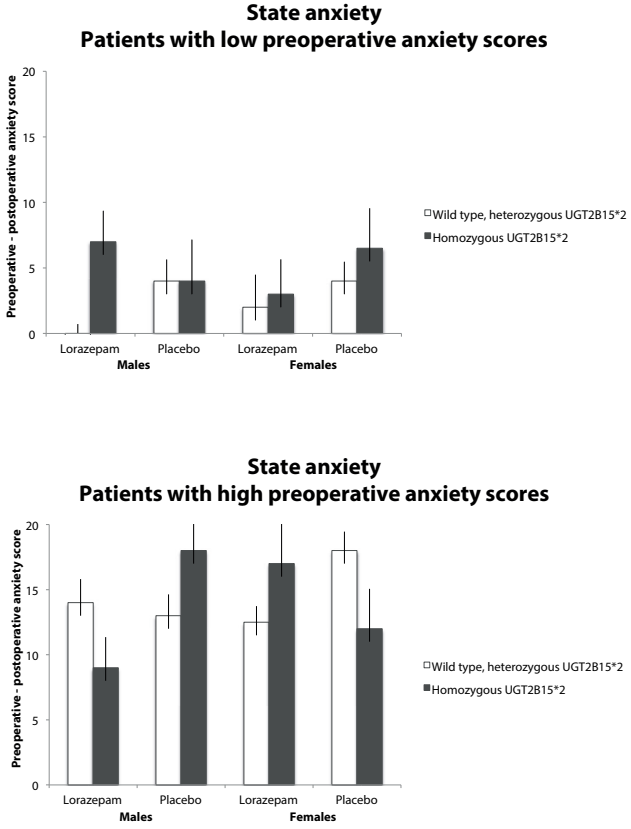

FIGURE 2 | STAI-State median difference for each patient category

The y-axis shows the median differences of the anxiety differences (i.e. preoperative anxiety score minus postoperative anxiety score). Positive median differences represent a decrease in anxiety postoperatively. Vertical bars represent standard errors according to that particular patient category.

Concerning postoperative anxiety reduction in patients treated with lorazepam, we expected more anxiety reduction in homozygous carriers of the *UGT2B15*2* genotype.[5] Therefore, of interest was the finding that anxiety reduction in females was almost 2 times greater compared with males with this genotype. Jackson et al[10] showed that sex differences after a single dosage of lorazepam is not likely because of pharmacokinetic differences and suggested that endogenous levels of neurosteroid hormones is a feasible explanation for the greater clinical effect of lorazepam in females. Moreover, one must take into account that levels of endogenous neurosteroid hormones, such as allopregnanolone, increase in stressful situations.[21] Allopregnanolone – a metabolite of the ovarian hormone progesterone – is one of the most potent endogenous neurosteroid hormones having the ability to positively modulate the γ-aminobutyric acid receptor type A.[22] Furthermore, it has been shown that allopregnanolone enhances the effects of benzodiazepine receptor agonists.[23-25]

Although explorative, this result may be of clinical relevance. It has been reported that almost half (49%) of the same-day surgery patients request preoperative anxiolytic premedication.[26] Administration of anxiolytic premedication traditionally focuses on the preoperative stress of a patient, but postoperative recovery has become of increasing importance, which has to be considered when the anesthesiologist decides to prescribe premedication. On the basis of recent randomized clinical trials,[9,27] anesthesiologists could negatively counsel patients in their preoperative assessment with respect to administration of premedication with lorazepam. However, our results might indicate that preoperative anxious females requesting premedication with lorazepam might benefit from *UGT2B15*2* genotyping because homozygous carriers show more postoperative anxiety reduction.

Study limitations

The results and application of the present study should be interpreted cautiously and within the context of the study methodology. Although we now have broader evidence that the *UGT2B15* genotype is not an independent determinant for the clinical effects of lorazepam, there could be still an explanation for this finding. First, this might be explained by the single dosage of intravenous lorazepam in this study. Second, the dosage of lorazepam administered could be too low to be influenced by *UGT2B15* genotype polymorphism. The very reason that we have refrained from administering a greater dosage was that it could provoke unwanted side effects such as drowsiness,[4] which would lead to delayed recovery which is not suitable for patients undergoing same-day surgery. Third, we refrained from significance testing on differences between the patient categories because of an insufficient number in these

patient categories and to avoid multiple testing (Appendix 1). Fourth, patients with low preoperative anxiety scores could have biased our results because those patients do not have the ability to show significant reduction in anxiety. In addition, although the analysis was adjusted for type of surgery and type of anesthesia to control for possible confounding, any medications given perioperatively and postoperative side-effects (e.g. nausea, drowsiness and pain) could still have biased the results and should be therefore subjected to further research. Fifth, because we do not have pharmacokinetic data in the present study, we assume that lorazepam plasma concentration differences have played a role. The rationale for studying the clinical effects of lorazepam on the *UGT2B15* genotype was the known significant association between lorazepam pharmacokinetics and the *UGT2B15* genotype.[5] Furthermore, in clinical practice, lorazepam is administered because of its clinical effects especially from a patient perspective. Sixth, our findings may not be necessarily extrapolated to other ethnic groups because it is known that ethnic origin could influence pharmacogenetics.[28] Our results are in line, however, with previous findings on other clinical effects of lorazepam according to *UGT2B15* genotype polymorphisms found in Korean people.[5] Furthermore, our study population has similar *UGT2B15* genotype frequencies compared with previous Caucasian populations studied.[29,30]

Future perspectives

Although it is known that pharmacogenetics influence the clinical response to perioperative drugs, routine screening prior to pharmacotherapy is still not cost-effective in clinical anesthesiology as we administer drugs to a large number of patients and frequently once only.[31] It is recommended, however, that clinical studies evaluating drug response in anesthesiology include pharmacogenetic testing.[31,32] Pharmacogenetic data obtained could be used, for example, for diagnostic purposes and risk stratification and could be of help to progress in new clinical studies in anesthesiology.[31]

In case of premedication with lorazepam, we cannot recommend routine screening of *UGT2B15* genotype at the moment. However, this study does define a population of clinical interest for future research. Future studies should be tailored to patients with high preoperative anxiety scores to gain more firm conclusions regarding the interaction between lorazepam and *UGT2B15* genotype on postoperative anxiety.

CONCLUSION

UGT2B15 genotype influences postoperative anxiety levels in same-day surgery patients receiving lorazepam premedication. In patients with high preoperative

anxiety scores treated with lorazepam, anxiety reduction was greater in females with the homozygous *UGT2B15*2* genotype compared to males with the same genotype polymorphism. To gain a deeper understanding in the clinical relevance of the interaction between lorazepam and *UGT2B15* genotype on postoperative anxiety levels, future studies—especially randomized clinical controlled trials—focussing on patients with high preoperative anxiety scores would be required.

APPENDIX 1 | Descriptive statistics of STAI-State distinguished by treatment condition, *UGT2B15* genotype polymorphism, patient sex and preoperative anxiety score

Patient category	Treat	UGT	Gender	*n*	Median	SE
1.	Lora	wt/ht	Male	38	-0.50	1.01
2.	Lora	hz	Male	20	7.00	1.22
3.	Plac	wt/ht	Male	59	4.00	0.76
4.	Plac	hz	Male	20	4.00	1.64
5.	Lora	wt/ht	Female	31	2.00	1.18
6.	Lora	hz	Female	7	3.00	2.48
7.	Plac	wt/ht	Female	24	4.00	1.12
8.	Plac	hz	Female	8	6.50	1.46
1.	Lora	wt/ht	Male	25	14.00	1.81
2.	Lora	hz	Male	15	9.00	2.36
3.	Plac	wt/ht	Male	23	13.00	1.64
4.	Plac	hz	Male	5	18.00	2.65
5.	Lora	wt/ht	Female	30	12.50	1.24
6.	Lora	hz	Female	13	17.00	3.16
7.	Plac	wt/ht	Female	34	18.00	1.46
8.	Plac	hz	Female	11	12.00	3.05

STAI-State = State-Trait Anxiety Inventory, State part; white = patients with low preoperative anxiety scores; grey = patients with high preoperative anxiety scores; Treat, treatment condition: Plac = Placebo (NaCl 0.9%), Lora = lorazepam; UGT = *UGT2B15* Genotype: wt/ht = wild type and heterozygous *UGT2B15*2*, hz = homozygous *UGT2B15*2*; *n* = number of patients; SE = standard error.

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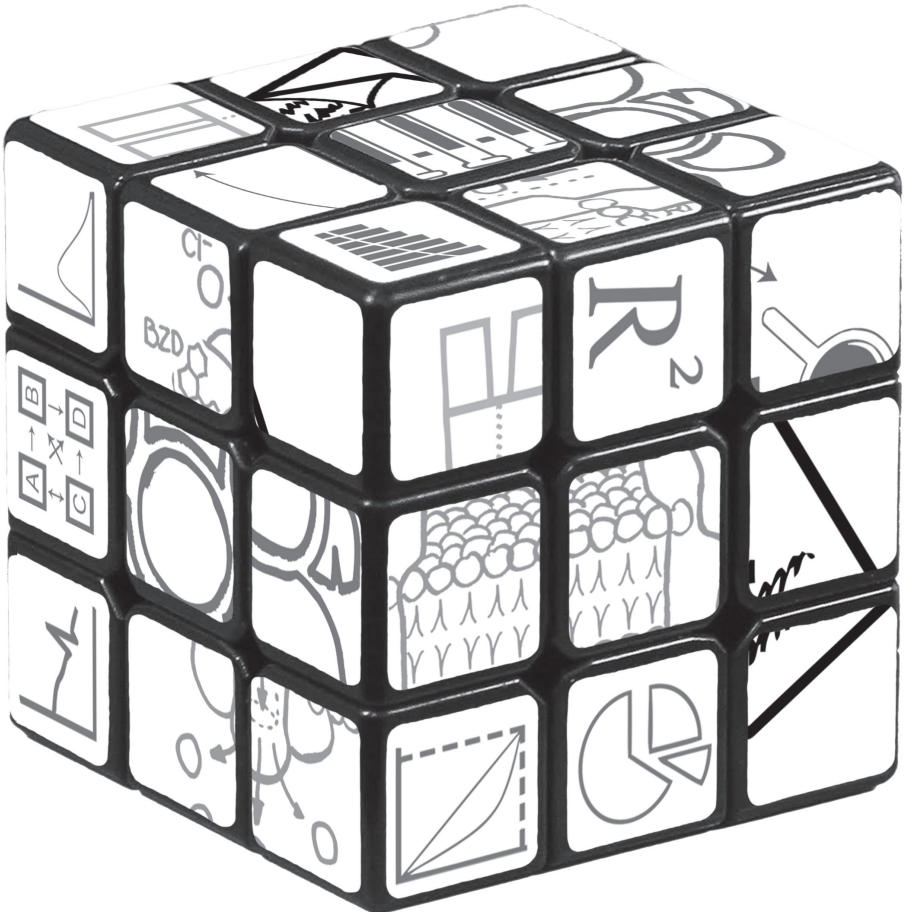
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EFFECTIVENESS OF BENZODIAZEPINE PREMEDICATION ON RECOVERY IN DAY-CASE SURGERY: A SYSTEMATIC REVIEW WITH META-ANALYSIS

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CHAPTER 4

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ABSTRACT

Benzodiazepines are frequently used as a premedication. In day-case surgery, anaesthetists are reluctant to administer benzodiazepines preoperatively for reasons of delayed recovery. However, premedication with benzodiazepines might be beneficial regarding postoperative somatic symptoms/complaints (i.e. time to recovery and postoperative side effects) and psychological phenomena. A systematic review with meta-analysis was performed using all important search engines. Study methodological quality was assessed using risk of bias tables. Mean differences (MD) and odds ratios (OR) were used for continuous data (time to recovery and psychological phenomena) and categorical data (postoperative somatic symptoms) respectively. Random effects modelling was applied. Nineteen studies were included. Overall time to recovery was significantly delayed in patients receiving benzodiazepines (MD 1.75; 95% CI 0.82 to 2.69) although time to discharge was not significantly affected. Postoperative side effects were significantly reduced in patients receiving benzodiazepines (OR 0.47; 95% CI 0.36 to 0.63). Regarding psychological outcome, only anxiety could be statistically analysed showing no statistical difference (MD 1.47; 95% CI -1.01 to 3.96). Although overall time to recovery was significantly prolonged by benzodiazepine premedication, withholding premedication in day-case surgery patients is not justified for such reason, as time to discharge was not negatively affected. Furthermore, benzodiazepines show to have beneficial effects on postoperative side effects. For firm conclusion regarding psychological phenomena, more research is needed. Anaesthetists should take into account this new evidence when they apply their premedication regime in day-case surgery.

INTRODUCTION

Benzodiazepines are among the most prescribed drugs used for premedication.[1] In a clinical setting, anaesthetists frequently administer benzodiazepines preoperatively as they have unique properties like anxiolysis – one of the main goals of premedication –, calming effects and anterograde amnesia as a favourable side effect profile.[1] Anaesthetists are reluctant to prescribe premedication (with benzodiazepines) in a day-case setting as patients could be too somnolent postoperatively. Consequently, this may prolong their time to discharge which should be avoided, especially, in day-case surgery. However, a Cochrane Review could not support this hypothesis,[2] although they did not focus specifically on benzodiazepine premedication. Furthermore, withholding premedication may not be justified as almost half of the patients in day-case surgery request something to relieve their stress and anxiety.[3]

In day-case surgery, patient's somatic symptoms became of minor interest as perioperative morbidity and mortality are extremely low.[4] Therefore, day-case surgery patients place higher priority on psychological phenomena rather than physical recovery in the postoperative period. Along with this, literature shows more attention for psychological aspects of perioperative care.[5,6] Research evaluating benzodiazepine administration in day-case surgery is focussing on psychological phenomena including anxiety, fatigue, aggression and depressive moods.[7]

Preoperative benzodiazepine administration is mostly evaluated preoperatively. However, the reluctance of anaesthetists is based on potential postoperative concerns. Therefore, to determine whether benzodiazepine premedication in day-case surgery is appropriate, thorough research focussing on the postoperative period is needed.

To evaluate the effectiveness of benzodiazepine administration in day-case surgery, we conducted a systematic review with meta-analysis of randomised trials focussing on postoperative somatic symptoms/complaints and psychological phenomena.

This systematic review and meta-analysis tested three related hypotheses:
1. In adult day-case surgery, benzodiazepines as a premedication do elongate time to recovery from general or regional anaesthesia;
2. Benzodiazepines as a premedication do beneficially affect postoperative somatic symptoms/complaints; and
3. Benzodiazepines as a premedication do reduce postoperative psychological sequelae.

METHODS

The *Preferred Reporting Items for Systematic Review and Meta-Analyses* guidelines were adhered to.[8]

Literature search

Literature search was performed in Embase, Medline OvidSP, ISI Web of Science, Scopus, Cochrane Central Register of Controlled Trials, PubMed Publisher, and Google Scholar, updated until January 2014. There were no language or publication date restrictions. Main key words for the search queries included day surgery, postoperative psychological aspect, somatic symptoms/complaints, and premedication. The full search is presented in Appendix 1.

Study selection

All randomised controlled trials including human adult patients undergoing day-case surgery were included when they really tested premedication. We defined 'premedication tested' as any medication given prior to induction of anaesthesia that was continued neither during the surgical procedure nor postoperatively. In addition, the intervention had to be tailored to the premedication itself. We excluded studies where no postoperative outcomes were assessed. Original articles written in English, German or French that included an abstract were maintained in the set in order to reduce language bias. Next, we excluded trials based on clinical anaesthetic and surgical selection criteria. Anaesthetic exclusion criteria concerned not undergoing general or regional anaesthesia. Surgical exclusion criteria included not undergoing day-case surgery or undergoing abortion, dental surgery or ophthalmology surgery. Also, trials testing non-benzodiazepines as a premedication were excluded. Finally, non-randomised studies and studies with no placebo control (i.e. methodological criteria) were excluded.

Data extraction and management

Three authors (HM, SVB, RJS) independently analysed studies for inclusion in the analysis. Two authors (HM, SVB) independently assessed all included studies with respect to their quality. Data was extracted using a pre-set collection sheet. Authors were not blinded for information regarding the identified studies (e.g. journal, author, institution, date of publication), as it was previously shown that not blinding did not influence the results of meta-analysis.[9] Disagreement among authors was resolved by consensus.
Included studies were reviewed for data on any of the following outcomes:

1. Somatic symptoms/complaints—*time to recovery*, time to eye opening, time to first correct response (TCR), time to early recovery (i.e. discharge form the recovery room) and time to discharge; *postoperative side effects*, including, nausea, vomiting/emesis, dizziness, pain, headache and miscellaneous (coughing and double vision).
2. Psychological outcomes—anxiety, depression, fatigue and aggression.

All outcomes were eligible for assessment when they were measured up to the first postoperative day.

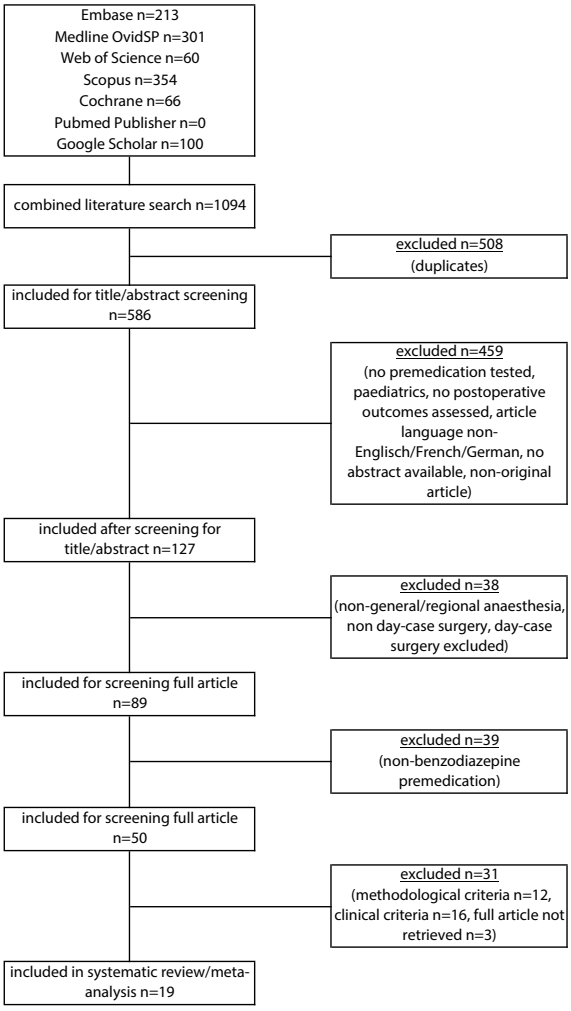


FIGURE 1| Flow of information

Quality assessment

The Cochrane Handbook of Systematic Reviews of Interventions was used to evaluate the risk of bias of each included study.[10] Selection-, performance-, detection-, attrition-, reporting- and other biases are assessed in this risk of bias tool.

Statistical Analysis

Categorical outcome data were evaluated by odds ratios (OR) while continuous outcome data were evaluated using mean differences (MD). Random effects model was used for each outcome. Meta-regression was performed in order to evaluate heterogeneity among studies and included the following covariates: year of publication, quality assessment and the journal's impact factor. Sensitivity analyses were performed in order to evaluate whether eliminating influential studies affect the results. Studies that exceed Cook's distance 1/*n* were found influential. Funnel plots were used to graphically examining small study effects as an asymmetrical funnel shape may indicate publication bias.[11] Inconsistency among studies was evaluated by means of the I^2-statistic. An I^2-statistic of 25%, 50% and 75% were respectively defined as low, moderate and high inconsistency.[12] We used Review Manager (RevMan) version 5.3 from the Cochrane Collaboration for analysis. Meta-regression was done in SPSS version 20.0 (IBM, NY, Armonk). Statistical significance was fixed at $P < 0.05$ (two-tailed).

RESULTS

Study selection and characteristics

The search was performed on 31 January 2014. After excluding duplicates ($n = 508$), 586 studies were screened on the base of title/abstract. Based on the selection criteria, clinical criteria and studies that did use benzodiazepines as a premedication we excluded 497 articles. Fifty full articles were reviewed accordingly. However, three articles could not be retrieved. We excluded 31 studies based on methodological and clinical criteria. Ultimately, 19 articles were eligible for systematic review/meta-analysis (Figure 1).[7,13-30] Table 1 shows the study characteristics. The risk of bias of the included studies is shown in Appendix 2. The risk of bias graph showing each risk of bias as percentages across all included studies is shown in Appendix 3. Appendix 4 shows the risk of bias scoring of the individual studies.

TABLE 1 | Characteristics of included studies

Reference	Methods	Participants	Intervention	Control	Outcomes	Notes
Abdul-Latif MS et al. (2001) [13]	Randomised placebo controlled double-blind study	50 female patients undergoing day case breast surgery, aged 18-70 years	7.5mg oral midazolam	Placebo	Somatic symptoms/complaints (time to recovery)	Source of funding not stated
Ahmed N et al. (1995) [14]	Randomised placebo controlleddouble-blinded study	50 mixed patients undergoing day-case surgery, aged 20-60 years	7.5mg oral midazolam	Placebo	Somatic symptoms/complaints (postoperative side effects); Psychological (anxiety)	Source of funding not stated
Bailie R et al. (1989) [15]	Randomised controlled trial	65 female patients undergoing day-case surgery, aged 16-75 years	20mg oral temazepam	Identical placebo capsule	Somatic symptoms/complaints (time to recovery)	Financially supported by Cognitive Drug Research
Bauer KP et al. (2004) [16]	Prospective randomised placebo-controlled study	88 mixed patients undergoing day-case surgery, aged 18-65 years	0.04mg/kg intravenous midazolam	Intravenous saline	Somatic symptoms/complaints (time to recovery; postoperative side effects); Psychological (anxiety)	Source of funding not stated
Beechey APG et al. (1981) [17]	Randomised placebo controlled double-blinded study	60 mixed patients undergoing elective minor surgery as day cases, aged 18-70 years	10mg oral temazepam	Identical placebo capsule	Somatic symptoms/complaints (time to recovery)	Source of funding not stated
Berendes E et al. (1996) [18]	Randomised placebo-controlled double-blinded study	85 female patients scheduled for breast biopsy	7.5mg oral midazolam; 20mg oral clorazepate dipotassium	Placebo	Psychological (anxiety, depression)	Source of funding not stated
De Witte JL et al. (2002) [19]	Randomised placebo controlled double blinded study	45 female patients undergoing day-case surgery, aged 18-50 years	0.5mg oral alprazolam; 7.5mg oral midazolam	Oral placebo	Somatic symptoms/complaints (time to recovery; postoperative side effects)	Financially supported by NIH Grant GM 58273, the Joseph Drown Foundation, and the Commonwealth of Kentucky Research Challenge Trust Fund

TABLE 1 | Characteristics of included studies (*continued*)

Reference	Methods	Participants	Intervention	Control	Outcomes	Notes
Duggan M et al. (2002) [20]	Randomised placebo controlled double-blinded study	61 mixed patients undergoing day-case surgery, aged 18-65 years	0.1mg/kg oral diazepam, 60 min preoperatively; 0.1mg/kg oral diazepam, 90 min preoperatively	Placebo	Psychological (anxiety)	Source of funding not stated
Forrest P et al. (1987) [21]	Randomised placebo controlled study	120 mixed patients undergoing day-case surgery; aged 20-60 years	0.25mg oral triazolam; 15mg oral midazolam; 10mg oral diazepam	Oral placebo	Somatic symptoms/ complaints (time to recovery)	Sources of funding not stated
Fredman B et al. (1999) [22]	Randomised placebo-controlled double-blinded study	90 patients undergoing brief procedures, aged 65-81 years	0.5mg intravenous midazolam; 2mg intravenous midazolam	Equal volume intravenous saline	Somatic symptoms/ complaints (time to recovery)	Source of funding not stated
Greenwood BK et al. (1983) [23]	Randomised placebo-controlled double-blinded study	72 mixed patients undergoing day-case surgery, aged 16-65 years	20mg oral temazepam; 30mg oral oxazepam	Placebo	Somatic symptoms/ complaints (time to recovery)	Source of funding not stated
Hargreaves J et al. (1988) [24]	Double-blinded study	90 mixed patients undergoing day-case surgery, aged 18-65 years	15mg oral midazolam; 20mg oral temazepam	Identical placebo	Somatic symptoms/ complaints (time to recovery)	Roche Products supplied the double-blind randomized premedications
Kain ZN et al. (2000) [25]	Randomised placebo-controlled double-blinded study	55 mixed patients undergoing day-case surgery, aged 18-60 years	5mg intramuscular midazolam	Intramuscular saline	Somatic symptoms/ complaints (time to recovery; postoperative side effects), Pyschological (anxiety)	Financially partly supported by a grant from the National institutes of Helat, Bethesda, Maryland, Roche Pharmaceuticals, Nutly, New Jersey, and the Patrick and Catherine Weldon Donaghue Medical Research Foundation, hartford, CT (Dr. Kain)

TABLE 1 | Characteristics of included studies (*continued*)

Reference	Methods	Participants	Intervention	Control	Outcomes	Notes
Loach A et al. (1975) [26]	Randomised placebo-controlled double-blinded study	22 female patients undergoing day-case surgery, aged 21-64 years	1mg oral lorazepam	Placebo	Somatic symptoms/complaints (postoperative side effects)	Source of funding not stated
Mijderwijk H et al. (2013) [7]	Randomised placebo-controlled double-blinded study	398 mixed patients undergoing day-case surgery, aged at least 18 years	1 to 1.5mg/ml intravenous lorazepam	1 to 1.5 ml intravenous saline	Psychological (anxiety, depression, fatigue, aggression)	Financial support was provided by the Department of Anaesthesiology, Erasmus University Medical Centre
Oxorn DC et al. (1997) [27]	Randomised placebo-controlled double-blinded study	60 female patients undergoing day-case surgery, aged >19 years	30ug/kg intravenous midazolam	0.03ml/kg intravenous saline	Somatic symptoms/complaints (time to recovery); Psychological (anxiety, depression, aggression)	Financial support was provided by a grant from Roche Pharmaceuticals and the First International Anesthesia Research Society Frontiers in Anesthesia Award
Raeder JC et al. (1987) [28]	Randomised placebo-controlled double-blinded study	193 female patients undergoing day-case surgery	0.1mg/kg intramuscular midazolam; 0.8 to 1ml intramuscular Mo-Scop (i.e. morphine 10mg/ml and scopolamine 0.4mg/ml)	0.8 to 1.0 ml intramuscular saline	Somatic symptoms/complaints (postoperative side effects)	Source of funding not stated
Raybould D et al. (1987) [29]	Randomised placebo-controlled double-blinded study	60 mixed patients undergoing day-case surgery; aged 16-65 years	7.5mg oral midazolam; 15mg oral midazolam	Placebo	Somatic symptoms/complaints (time to recovery)	Source of funding not stated
Shafer A et al. (1989) [30]	Randomised placebo-controlled double-blinded study	150 mixed patients undergoing day-case surgery, aged 15-41 years	5mg (1ml) intramuscular midazolam; 1mg (2ml) intravenous oxymorphone; 100ug (2ml)	1ml intramuscular saline; 2ml intravenous saline	Somatic symptoms/complaints (time to recovery; postoperative side effects)	Source of funding not stated

Somatic symptoms/complaints—time to recovery

Twelve studies were included in meta-analysis with 1445 patients altogether.[13,15,16,19,21-25,27,29,30] Applying random effects model resulted into $Tau^2 = 2.78$, $Chi^2 = 69.73$, df = 26, $P < 0.01$, $I^2 = 63\%$. Overall time to recovery was significantly delayed by benzodiazepines with 1.75 minutes (95% CI 0.82 – 2.69) (Figure 2a). Time to eye opening was significantly delayed with 1.47 minutes by benzodiazepines (95% CI 0.51 – 2.42), but we could not find statistical significant differences regarding time to first correct response ($P = 0.06$), time to early recovery ($P = 0.24$) and time to discharge ($P = 0.39$), Figure 2a. Sensitivity analyses did not provide new insights. None of the covariates could explain the heterogeneity among the studies for time to eye opening, early recovery and discharge. However, time to first correct response (TCR) increased significantly in studies with a higher methodological quality (Appendix 5). All funnel plots of these studies were not considered asymmetrical (Appendix 6a).

In addition, Beechey *et al*., Hargreaves and Raybould *et al*. could not be subjected to meta-analyses but did report on time to recovery.[17,24,29,31] Beechey et al. found no difference in the time to awaken from anaesthesia.[17,31] Hargreaves found that awakening from anaesthesia was significantly longer in the midazolam group compared to placebo and temazepam groups.[24] Raybould *et al*. showed that the group receiving a benzodiazepine did not show significantly longer recovery times.[29]

Somatic symptoms/complaints—postoperative side effects

Seven studies were included in meta-analysis with 1530 patients altogether.[14,16,17,23,26,28,30]Results of random effects model yielded $Tau^2 = 0.00$, $Chi^2 = 19.25$, df = 24, $P = 0.74$, $I^2 = 0\%$. Overall postoperative side effects occurred significantly less in patients treated with benzodiazepines (OR 0.47, 95% CI 0.36 – 0.63) (Figure 2b).

Nausea (OR 0.34, 95% CI 0.21 – 0.55) and headache (OR 0.44, 95% CI 0.25 – 0.78) occurred significantly less in the patients treated with benzodiazepines. However, we could not find statistical significant differences regarding vomiting ($P = 0.08$), dizziness ($P = 0.68$) and the miscellaneous group ($P = 0.21$). Categorical data regarding pain showed no statistical significant difference ($P = 0.86$) as well as pain scored on a continuous scale ($P = 0.55$).

In addition, de Witte *et al*., Hargreaves and Kain *et al*. could not be subjected to meta-analyse but did report postoperative side effects.[19,24,25] De Witte *et al*. found no statistical difference in the incidence of nausea or vomiting and other side effects including

dizziness and headache.[19] Hargreaves found no statistical difference in the incidence of minor side effects.[24] However, nausea was found in 8 patients receiving temazepam, which was statistically significant when compared to the placebo group. Kain *et al*. found no significant difference regarding a postoperative pain score (Visual Analogue Score [VAS] >30) on discharge form the Post Anaesthesia Care Unit (PACU).[25] Furthermore, undefined adverse effects were not significantly different in PACU.

Sensitivity analysis and meta-regression did not provide new insights (Appendix 5). Funnel plot for dizziness was asymmetrical suggesting publication bias; the other funnel plots were considered symmetrical (Appendix 6b).

Psychological outcomes

A total of 4 studies assessing anxiety were included in meta-analysis with 653 patients.[7,25,27,30] Random effects model yielded $Tau^2 = 3.96$, $Chi^2 = 15.33$, $df = 3$, $P < 0.01$, $I^2 = 80\%$. Anxiety was not significantly affected (mean difference 1.47, 95% CI -1.01 – 3.96) (Figure 2c).

Ahmed *et al*., Bauer *et al*., Berendes *et al*., de Witte *et al*., Duggan *et al*. and Fredman *et al*. could not be subjected to meta-analysis but did report on anxiety.[14,16,18-20,22] Ahmed *et al*. found no significant difference in patient's anxiety levels.[14] Bauer *et al*. did not found statistical significant difference in patient's anxiety levels in PACU and at discharge from PACU.[16] Berendes *et al*. found that clorazepate dipotassium had significant lower anxiety scores compared to placebo.[18] No significant difference was found between midazolam and placebo. De Witte *et al*. found that all patients in the midazolam group reported a sufficient quality of anxiety reduction; 2 patients in the alprazolam group reported insufficient anxiety reduction and 1 patient did not know; 7 patients in the placebo group reported insufficient anxiety reduction and 3 patient did not know, which was statistically significant among groups.[19] Duggan *et al*. found no significant difference in anxiety scores (VAS and State part of the State-Trait Anxiety Inventory (STAI-State)) at discharge.[20]Fredman *et al*. found that anxiety scores were unaffected during PACU admission.[22]

The studies by Kain *et al*. and Mijderwijk *et al*. measured anxiety beyond the first postoperative day.[7,25] Kain *et al*. found a significant greater reduction in anxiety in the benzodiazepine group compared with placebo from 2-30 days after surgery.[25] Mijderwijk *et al*., on the seventh day after surgery, found significant greater reduction in anxiety measured by means of the Trait part of the State-Trait Anxiety Inventory (STAI-Trait) and by means of the Hospital Anxiety and Depression Scale (HADS) in the placebo

group, although no significant result was found regarding STAI-state.[7]

None of the covariates enabled explaining heterogeneity among the studies (Appendix 5). Sensitivity analyses did not provide new insights. The funnel plot was not considered asymmetrical (Appendix 6c).

Only the studies by Mijderwijk *et al*. and Oxorn *et al*. have reported about depression, fatigue and aggression.[7,27] Oxorn *et al*. have reported results up to first postoperative day.[27] They found no significant differences on depression and aggression while Mijderwijk *et al*. measured these outcomes beyond the first postoperative day.[7] Although no significant differences were found on depression, fatigue and trait aggression on the seventh day after surgery, yet they found a statistically significant result regarding state aggression.

DISCUSSION

Principal finding

The principal finding of this systematic review with meta-analysis is that overall benzodiazepines did unfavourably affect time to recovery, did reduce the incidence of postoperative side effects but they did not statistically significantly affect psychological outcomes. These findings will be discussed in further detail below.

Time to recovery

The overall test of significance showed that time to recovery is significantly prolonged in patients administered benzodiazepines preoperatively. However, only time to eye opening is significantly prolonged by 1.47 minutes in the benzodiazepine group. Time to early recovery and time to discharge were not affected by benzodiazepines. Although not statistically significant, benzodiazepines tend to prolong TCR. The articles that could not be subjected to meta-analysis are considered to have no influence.[17,24,29]

Considering all this, we agree with (some) anaesthetists that recovery time is prolonged by benzodiazepines but only at the first stage of recovery. Time to early recovery and time to discharge are clearly not affected by benzodiazepine premedication which is in line with a previous review.[2] Therefore, withholding benzodiazepine premedication for reasons of delayed discharge time seems not justified in day-case surgery.

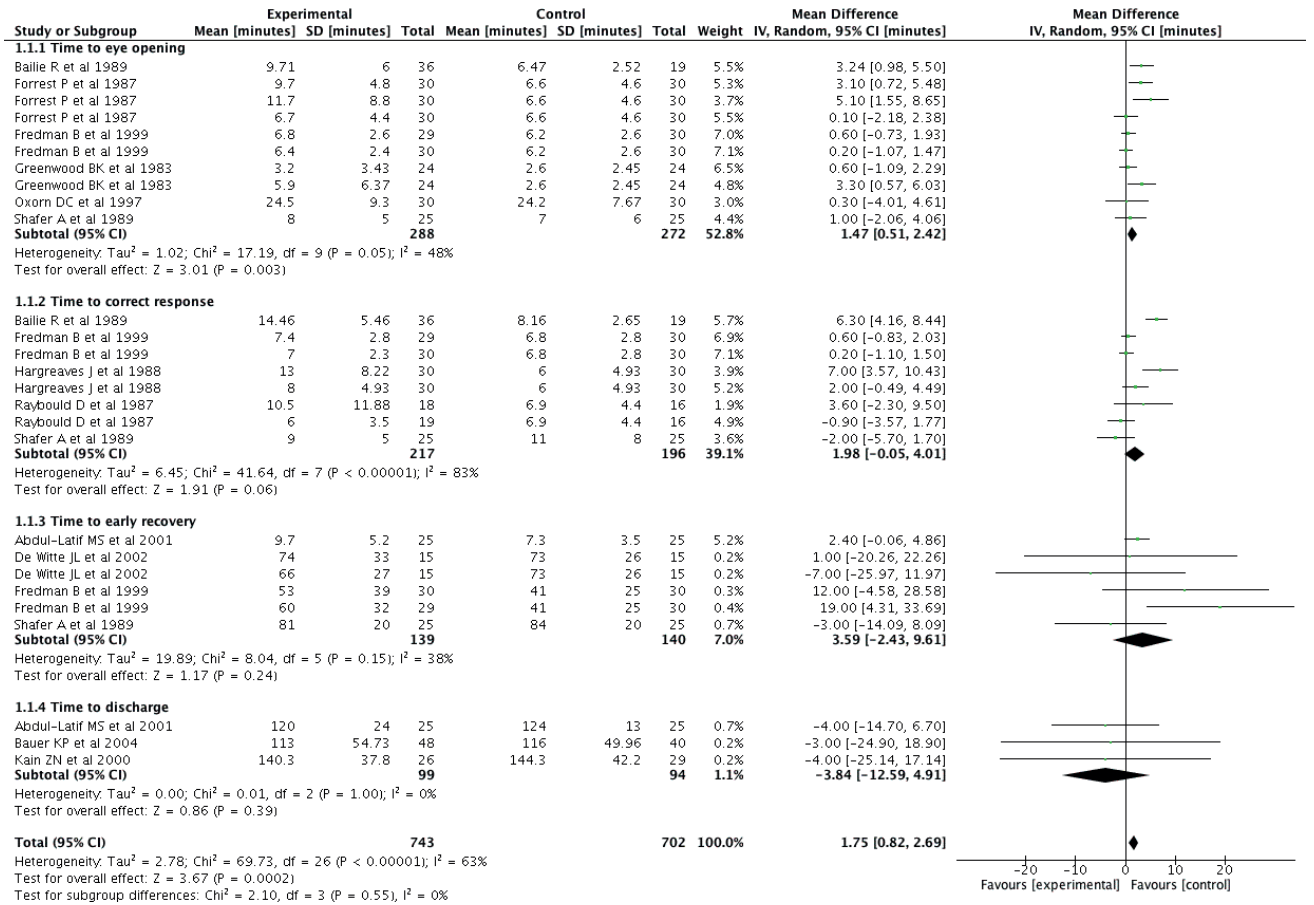


FIGURE 2 | Forest plot for time to recovery

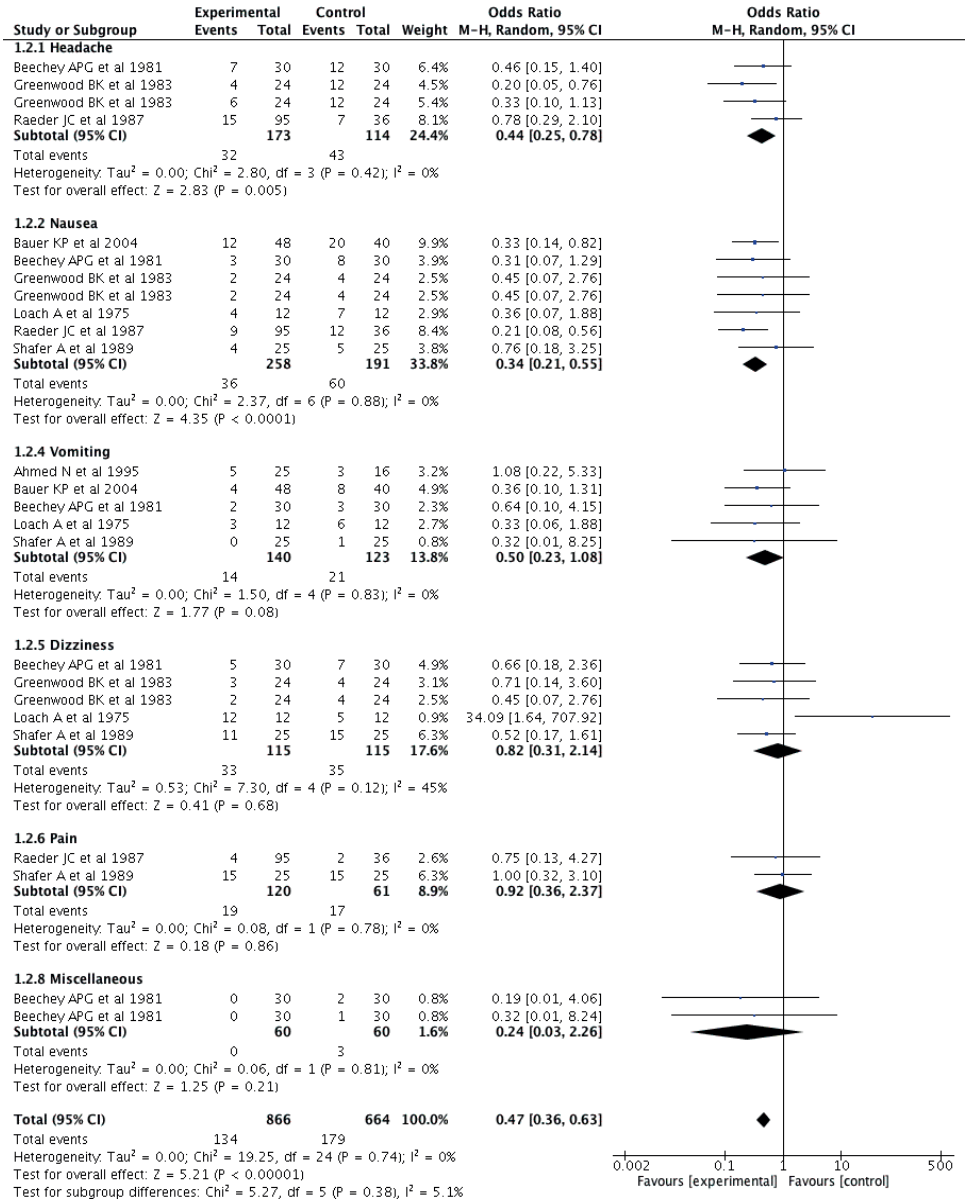


FIGURE 2B | Forest plots for postoperative side effects (1/2)
Regarding Raeder JC et al., postoperative n was determined proportionally and data regarding 'nausea at home' was ignored as this data is likely correlated with 'nausea at recovery'.

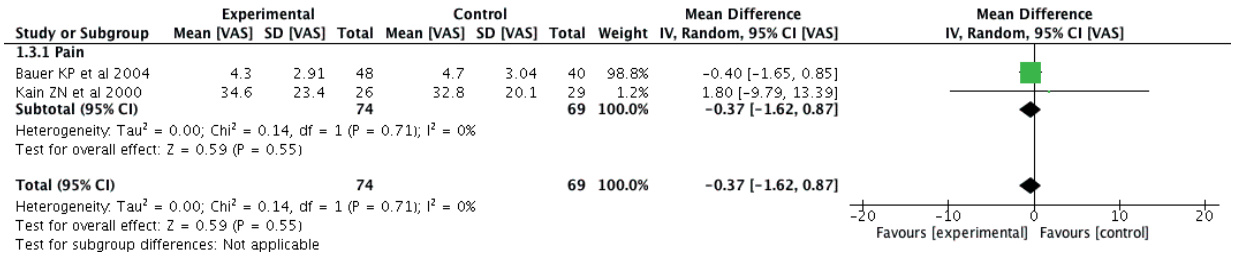


FIGURE 2B | Forest plots for postoperative side effects (2/2)
Regarding Raeder JC et al., postoperative n was determined proportionally and data regarding 'nausea at home' was ignored as this data is likely correlated with 'nausea at recovery'.

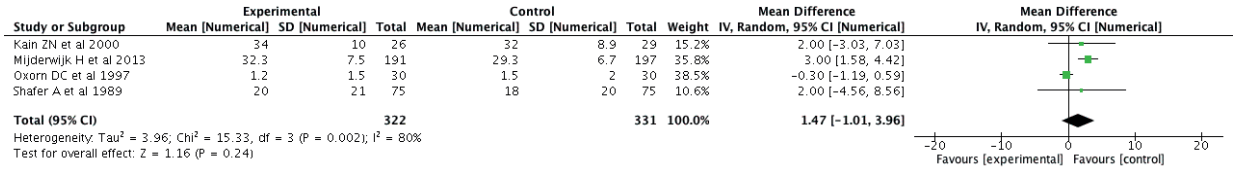


FIGURE 2C | Forest plot for psychological phenomena (anxiety)

Postoperative side effects

The overall test of significance showed that premedication with benzodiazepines significantly reduced the incidence of postoperative side effects with 53%. When looking into further detail, benzodiazepine premedication clearly reduces the risk of postoperative headache (56%) and nausea (66%), and show a tendency to reduce the risk of vomiting. The risk of postoperative dizziness, pain and miscellaneous side effects was not statistically significantly affected by benzodiazepines. The articles not meeting the standards for this meta-analysis are considered to have no influence.[19,24,25]

After discharge from day-case surgery, headache, nausea and vomiting emerge with incidence rates of 27%, 17-21% and 5.7-8% respectively.[32,33] Benzodiazepine premedication could be a favourable way to reduce these postoperative side effects, and, consequently, enhancing the quality of patients' somatic recovery. We are fully aware that with regards to postoperative somatic symptoms/complaints, more factors could emerge in the postoperative period, such as sore throat and back pain.[32,33] Unfortunately, due to lack of data we could not test for these factors with regards to benzodiazepine premedication. This could be subject of further research.

Psychological phenomena

We were able to perform meta-analysis for anxiety, showing no statistical significant differences between benzodiazepine or placebo groups. With regards to the other psychological outcomes (i.e. depression, aggression and fatigue), meta-analysis could not be performed at all as they did not meet the eligibility criteria with regards to the time span. Therefore, the effects of premedication with benzodiazepines on psychological phenomena remain inconclusive. Given the shift towards psychological outcome in day-case surgery,[5-7] we need more research on this topic. This should also be studied beyond the first postoperative day as recommend by others.[32] Furthermore, we need more research on interventions in the preoperative period that could beneficially affect the postoperative period.[34]

Methodological strengths and weaknesses

The rationale for our extensive literature search was to get a solid understanding of the effects of benzodiazepine premedication in day-case surgery patients regarding somatic symptoms/complaints and psychological phenomena emerging in the postoperative period. By doing so, we minimized the risk of selection bias too. As a consequence, we had to evaluate many studies for eligibility. Selection bias was also minimized by not excluding studies based on their quality assessment. We tried to minimize language bias

by including articles not only written in English but also in German and France, when appropriate. This strategy seems justified as we included an article written in German.[18] However, potential language bias could not be ruled out. We were able to check the possible influence of the year of publication on the outcomes, as we did not have year of publication restrictions in our literature search. We used a pre-set standardized form for data-extraction and management. Risk of bias tables were used to evaluate the quality of each study, which was done by two authors individually. Discrepancies were resolved by consensus. Meta-regression was performed on each outcome individually. Meta-regression was not always possible as numerical data was not always clearly provided or not provided. To deal with this, we systematically described the results of the outcomes of these studies.

Random effects model was performed for each meta-analysis when heterogeneity was present. For consistency's sake, we also performed random effects model when heterogeneity was statistically not significant. Another justification for this analysis strategy is that judgements for heterogeneity in meta-analysis can be misleading when the number of included patients is insufficient.[35] Thus we possibly could have under-estimated heterogeneity and therefore we have applied random effects model even when heterogeneity was statistically insignificant.

The fact that heterogeneity is predominantly present in time to recovery and psychological phenomena while heterogeneity is nearly present in postoperative side effects suggests that the assessment sources may be different. With regards to time to recovery, in the majority of the studies it is unclear who actually measured time to recovery. However, in the study by De Witte *et al*. study nurses observed the patients in the recovery room.[19] Likely, although not specifically stated, they assessed time to early recovery. Accordingly, interjudgement unreliability bias may have emerged and this could be the reason for the wide confidence intervals of this particular study. On the other hand, intrajudgement unreliability may have played a role when, for example, the pre-set definitions for specific time to recovery were not clear. Furthermore, next to these within study variation, in between study heterogeneity is possibly caused by intra- and/or interjudgement bias. Physicians, nurses or investigators may have alternately assessed time to recovery in patients, which is likely to induce bias.

The moderate inconsistency regarding dizziness can be caused by the vague definition of dizziness interpreted by patients. However, it was previously shown that heterogeneity might also be due to publication bias[36] (i.e. small studies with expressive results are likely to be published) and in the case of dizziness publication bias has emerged.

Heterogeneity can also be present due to conceptual concerns, especially in case of psychological outcomes. For example, anxiety itself can be considerably heterogeneous and reasons for heterogeneity can be difficult to clarify.[37] Furthermore, heterogeneity among studies may always be due to change.[11]

In this study, we have focussed on a homogenous group of drugs used for premedication. As a consequence, we were able to perform meta-analysis and could draw conclusions from our results accordingly. Such a statistical synthesis was previously not feasible due to too many different premedication drugs.[2] A total of eight different benzodiazepines, three different administration routes and different times of administration were nonetheless present in our meta-analysis. Unfortunately, it was methodologically statistically not feasible to evaluate this possible heterogeneity in our meta-regression. However, administration of benzodiazepines is characterized by high efficacy despite differences in route of administration and pharmacological properties.

CONCLUSION

This systematic review with meta-analysis provides new evidence for beneficial effects of premedication with benzodiazepines in day-case surgery. Benzodiazepine premedication does prolong time to recovery but only at the first stage of postoperative recovery – time to discharge is not affected. Furthermore, benzodiazepines seem to reduce the incidence of postoperative side effects with 53%. However, effects on psychological outcomes remain inconclusive. It is recommended that future studies should also focus on other postoperative side effects, and on psychological phenomena.

ACKNOWLEDGEMENT

We thank Wichor M. Bramer, information specialist at Erasmus MC, for performing the literature search.

APPENDICES

APPENDIX 1 | Complete literature search, 31 January 2014

Embase	213	210
Medline OvidSP	301	157
Web-of-science	60	26
Scopus	354	119
Cochrane	66	6
PubMed publisher	0	0
Google Scholar	100	68
Total	1094	586
Duplicates removed: 508		

Embase

('ambulatory surgery'/de OR (((ambul* OR day OR daycare OR daycase OR outpatient* OR office*) NEAR/3 (surg* OR operati*))):ab,ti) AND ('psychological aspect'/de OR psychology/exp OR emotion/exp OR depression/exp OR fatigue/de OR exhaustion/de OR stress/exp OR 'adaptive behavior'/de OR 'surgical stress'/de OR (psycholog* OR emotion* OR anxiet* OR fatigue OR exhaust* OR depress* OR perception* OR (somatic NEAR/3 (symptom* OR complain*)) OR ((mental OR preoperat* OR postoperat* OR perioperat* OR operative* OR surg*) NEXT/1 stress) OR (adapt* NEAR/3 behavio*) OR coping):ab,ti) AND (adult/exp OR 'middle aged'/de OR aged/exp OR (adult* OR aged):ab,ti) AND (premedication/de OR benzodiazepine/de OR 'anesthetic agent'/exp OR 'antidepressant agent'/exp OR tranquilizer/exp OR (premedicat* OR pretreatment* OR (pre NEXT/1 (medicat* OR treatment*)) OR preanesthe* OR preanaesthe* OR anaesthetic* OR anesthetic* OR ((anxiet* OR antianxiet* OR ataract*) NEAR/3 (agent* OR drug*)) OR benzodiazepine* OR anxiolytic* OR tranquill* OR antidepress*):ab,ti) AND ((random* OR factorial* OR crossover* OR (cross NEXT/1 over*) OR placebo* OR ((doubl* OR singl*) NEXT/1 blind*) OR assign* OR allocat* OR volunteer*):ab,ti OR 'crossover procedure'/de OR 'double-blind procedure'/de OR 'randomized controlled trial'/de OR 'single-blind procedure'/de) NOT ([animals]/lim NOT [humans]/lim)

Medline OvidSP

("Ambulatory Surgical Procedures"/ OR (((ambul* OR day OR daycare OR daycase OR outpatient* OR office*) ADJ3 (surg* OR operati*))).ab,ti.) AND (exp psychology/ OR psychology.xs. OR exp emotions/ OR depression/ OR exp fatigue/ OR "Stress,

Psychological"/ OR "Adaptation, Psychological"/ OR "surgical stress"/ OR (psycholog* OR emotion* OR anxiet* OR fatigue OR exhaust* OR depress* OR perception* OR (somatic ADJ3 (symptom* OR complain*)) OR ((mental OR preoperat* OR postoperat* OR perioperat* OR operative* OR surg*) ADJ stress) OR (adapt* ADJ3 behavio*) OR coping).ab,ti.) AND (exp adult/ OR (adult* OR aged).ab,ti.) AND (premedication/ OR "Preanesthetic Medication"/ OR exp benzodiazepines/ OR exp "anesthetics"/ OR exp "antidepressive agents"/ OR exp "Tranquilizing Agents"/ OR (premedicat* OR pretreatment* OR (pre ADJ (medicat* OR treatment*)) OR preanesthe* OR preanaesthe* OR premedicat* OR pretreatment* OR preanesthe* OR preanaesthe* OR anaesthetic* OR anesthetic* OR ((anxiet* OR antianxiet* OR ataract*) ADJ3 (agent* OR drug*)) OR benzodiazepine* OR anxiolytic* OR tranquill* OR antidepress*).ab,ti.) AND (Clinical Trial.pt. OR randomized.ab,ti. OR placebo.ab,ti. OR dt.fs. OR randomly.ab,ti. OR trial.ab,ti. OR groups.ab,ti. NOT (Animals/ NOT Humans/))

Cochrane

((((ambul* OR day OR daycare OR daycase OR outpatient* OR office*) NEAR/3 (surg* OR operati*))):ab,ti) AND ((psycholog* OR emotion* OR anxiet* OR fatigue OR exhaust* OR depress* OR perception* OR (somatic NEAR/3 (symptom* OR complain*)) OR ((mental OR preoperat* OR postoperat* OR perioperat* OR operative* OR surg*) NEXT/1 stress) OR (adapt* NEAR/3 behavio*) OR coping):ab,ti) AND ((adult* OR aged):ab,ti) AND ((premedicat* OR pretreatment* OR (pre NEXT/1 (medicat* OR treatment*)) OR preanesthe* OR preanaesthe* OR anaesthetic* OR anesthetic* OR ((anxiet* OR antianxiet* OR ataract*) NEAR/3 (agent* OR drug*)) OR benzodiazepine* OR anxiolytic* OR tranquill* OR antidepress*):ab,ti)

Web-of-science

TS=(((((ambul* OR day OR daycare OR daycase OR outpatient* OR office*) NEAR/3 (surg* OR operati*)))) AND ((psycholog* OR emotion* OR anxiet* OR fatigue OR exhaust* OR depress* OR perception* OR (somatic NEAR/3 (symptom* OR complain*)) OR ((mental OR preoperat* OR postoperat* OR perioperat* OR operative* OR surg*) NEXT/1 stress) OR (adapt* NEAR/3 behavio*) OR coping)) AND ((adult* OR aged)) AND ((premedicat* OR pretreatment* OR (pre NEXT/1 (medicat* OR treatment*)) OR preanesthe* OR preanaesthe* OR anaesthetic* OR anesthetic* OR ((anxiet* OR antianxiet* OR ataract*) NEAR/3 (agent* OR drug*)) OR benzodiazepine* OR anxiolytic* OR tranquill* OR antidepress*)) AND (random* OR factorial* OR crossover* OR (cross NEAR/1 over*) OR placebo* OR ((doubl* OR singl*) NEAR/1 blind*) OR assign* OR allocat* OR volunteer*))

Scopus

TITLE-ABS-KEY(((((ambul* OR day OR daycare OR daycase OR outpatient* OR office*) W/3 (surg* OR operati*)))) AND ((psycholog* OR emotion* OR anxiet* OR fatigue OR exhaust* OR depress* OR perception* OR (somatic W/3 (symptom* OR complain*)) OR ((mental OR preoperat* OR postoperat* OR perioperat* OR operative* OR surg*) PRE/1 stress) OR (adapt* W/3 behavio*) OR coping)) AND ((adult* OR aged)) AND ((premedicat* OR pretreatment* OR (pre PRE/1 (medicat* OR treatment*)) OR preanesthe* OR preanaesthe* OR anaesthetic* OR anesthetic* OR ((anxiet* OR antianxiet* OR ataract*) W/3 (agent* OR drug*)) OR benzodiazepine* OR anxiolytic* OR tranquill* OR antidepress*)) AND (random* OR factorial* OR crossover* OR (cross W/1 over*) OR placebo* OR ((doubl* OR singl*) W/1 blind*) OR assign* OR allocat* OR volunteer*))

PubMed publisher

((((ambul*[tiab] OR day[tiab] OR daycare[tiab] OR daycase[tiab] OR outpatient*[tiab] OR office*[tiab]) AND (surger*[tiab] OR surgic*[tiab] OR operati*[tiab])))) AND ((psycholog*[tiab] OR emotion*[tiab] OR anxiet*[tiab] OR fatigue[tiab] OR exhaust*[tiab] OR depress*[tiab] OR perception*[tiab] OR (somatic symptom*[tiab] OR somatic complain*[tiab] OR ((mental stress[tiab] OR preoperative stress[tiab] OR postoperative stress[tiab] OR perioperative stress[tiab] OR operative stress[tiab] OR surgical stress[tiab])) OR (adaptive behavio*[tiab]) OR coping)) AND ((adult*[tiab] OR aged[tiab])) AND ((premedicat*[tiab] OR pretreatment*[tiab] OR pre medicat*[tiab] OR pre treatment*[tiab] OR preanesthe*[tiab] OR preanaesthe*[tiab] OR anaesthetic*[tiab] OR anesthetic*[tiab] OR ((anxiet*[tiab] OR antianxiet*[tiab] OR ataract*[tiab]) AND (agent*[tiab] OR drug[tiab] OR drugs[tiab])) OR benzodiazepine*[tiab] OR anxiolytic*[tiab] OR tranquill*[tiab] OR antidepress*[tiab]) AND (random*[tiab] OR factorial*[tiab] OR crossover*[tiab] OR cross over*[tiab] OR placebo*[tiab] OR double blind*[tiab] OR single blind*[tiab] OR assign*[tiab] OR allocat*[tiab] OR volunteer*[tiab])) AND publisher[sb]

Google Scholar

“ambulatory|day|daycare surgery|operation”

APPENDIX 2 | Risk of bias table – authors' judgement

Reference	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Abdul-Latif MS et al.[13]	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Unclear risk
Support for judgement	Comment: not reported whether random sequence generation was performed.	Comment: not reported whether allocation concealment was achieved.	Comment: anaesthetists were blinded as well as the patients.	Comment: not reported whether time to recovery was blindly assessed.	Comment: table 2 shows that all patients were assessed for time to recovery.	Comment: all measures with respect to time to recovery were presented.	Comment: no other sources of bias identified
Ahmed N et al.[14]	Unclear risk	Unclear risk	Low risk	Low risk	High risk	Low risk	High risk
Support for judgement	Quote: "..patients..were randomly allocated to receive either Midazolam 7.5 mg or a placebo.." Comment: insufficient information about the sequence generation process.	Comment: not reported whether allocation concealment was achieved.	Quote: "The study was done in a double blind manner."	Quote: "The anaesthetist involved in recording observations was unaware of the patient grouping."	Comment: 9 patients are excluded from the analyses. Reasons for the exclusions are not given. Furthermore, it is likely that these missings all belong to the placebo group, and, consequently, imbalancedness is likely to emerge.	Comment: all outcomes are reported as dictated by the study protocol as written in the Methods section.	Comment: the groups are imbalanced regarding sex: the male/female ratio for the midazolam group equals 2/3, whereas the ratio for the placebo group equals 15/1.
Bailie R et al.[15]	High risk	Low risk	Low risk	Unclear risk	High risk	Low risk	Unclear risk
Support for judgement	Quote: "The hospital pharmacist, who was not involved in the study, had previously allocated them to one of two groups." However: "Because of a delay in obtaining matched placebo capsules, the first 26 patients of 65 patients were allocated to group 1."	Quote: "..was unknown to the researcher undertaking the cognitive assessments and to those conducting initial evaluation of data."	Quote: "All testing and initial evaluation of data was conducted double-blind."	Comment: not reported if time to recovery was blindly assessed.	Quote: "Six patients in the placebo group were withdrawn. Four patients in the temazepam group were withdrawn. Comment: Imbalancedness emerged: >20% withdrawn	Comment: all outcomes are reported as dictated by the study protocol as written in the Methods section.	Comment: no other sources of bias identified.

APPENDIX 2 | Risk of bias table – authors' judgement *(continued)*

Reference	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bauer KP et al.[16]	Unclear risk	Low risk	Low risk	Low risk	High risk	Low risk	Unclear risk
Support for judgement	Comment: not reported whether random sequence generation was performed.	Quote: "Study syringes were prepared by the pharmacy. Patients, anesthesiologists, and investigators were blinded to the contents of each syringe until the study was completed."	Quote: "Patients, anesthesiologists, and investigators were blinded to the contents of each syringe until the study was completed."	Quote: "Patients, anesthesiologists, and investigators were blinded to the contents of each syringe until the study was completed."	Quote: "..a total of 118 patients signed a consent form. Of that number, 13 patient were withdrawn from data analysis for protocol violations, and 17 patients were withdrawn from data analysis because of missing data." Comment: no reasons for missing data provided.	Comment: all outcomes are reported as dictated by the study protocol as written in the Methods section.	Comment: no other sources of bias identified.
Beechey APG et al.[17]	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Unclear risk
Support for judgement	Quote: "The patients, who gave informed consent, were randomly allocated into two groups.." Comment: insufficient information about the sequence generation process.	Comment: not reported how allocation concealment was achieved.	Quote: "A double-blind trial was therefore undertaken.." "..placebo capsules of identical appearance were used.."	Comment: not reported whether blinding of outcome assessment was achieved.	Comment: no missing outcome data.	Comment: all outcomes are reported as dictated by the study protocol as written in the Methods section.	Comment: no other sources of bias identified.

APPENDIX 2 | Risk of bias table – authors' judgement *(continued)*

Reference	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Berendes E et al.[18]	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Unclear risk
Support for judgement	Quote: "Die Randomisierung in 3 Gruppen erfolgte anhand einer Tabelle mit Zufallszahlen."	Quote: "Zwei Stunden präoperative erhielten die Patientinnen in einem verschlossenen un numerierten Umschlag entweder..Midazolam,.. Dikaliumclorazepat oder ein Plazebopräparat.."	Quote: "Die Studie wurde als prospektive randomisierte Doppelblindstudie durchgeführt."	Comment: unclear if blinding of outcome assessment was achieved.	Comment: no missing outcome data.	Comment: all outcomes are reported as dictated by the study protocol as written in the Methods section.	Comment: no other sources of bias identified.
De Witte JL et al.[19]	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Unclear risk
Support for judgement	Quote: "..patients were randomly assigned to receive.." Comment: insufficient information about the sequence generation process.	Comment: not reported how allocation concealment was achieved.	Quote: "..outpatients participated in a double-blinded study.."".the commercially available drug tablets were placed in opaque capsules filled with an inactive powder."	Comment: not reported whether blinding of outcome assessment was achieved.	Comment: no missing outcome data.	Comment: all outcomes are reported as dictated by the study protocol as written in the Methods section.	Comment: no other sources of bias identified.

APPENDIX 2 | Risk of bias table – authors' judgement *(continued)*

Reference	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Duggan M et al.[20]	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Unclear risk
Support for judgement	Quote: "Randomization was performed using a random numbers table."	Quote: "Randomization was performed using a random numbers table by the research division, pharmacy, Beaumont Hospital." Comment: central allocation.	Quote: "We conducted a..double-blind, randomized study.."".Group III received a placebo."	Comment: not reported whether blinding of outcome assessment was achieved.	Quote: "One patient was excluded as she required admission to the hospital overnight.." Comment: this missing data was judged to have no clinical impact.	Comment: all outcomes are reported as dictated by the study protocol as written in the Methods section.	Comment: no other sources of bias identified.
Forrest P et al.[21]	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Unclear risk
Support for judgement	Quote: "..patients were randomly allocated to receive..one of four oral premedicants from coded envelopes.." Comment: insufficient information about the sequence generation process.	Comment: not reported how allocation concealment was achieved.	Quote: "Patients were randomly allocated to receive, in a double-blind manner.."	Comment: not reported whether blinding of outcome assessment was achieved.	Comment: no missing outcome data relative to time to recovery. However, some missing data in other parts of the study; unclear if this leads to risk of bias.	Comment: all outcomes are reported as dictated by the study protocol as written in the Methods section.	Comment: no other sources of bias identified.
Fredman B et al.[22]	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Support for judgement	Quote: "computer-generated randomization table".	Comment: not reported how allocation concealment was achieved.	Quote: "90 geriatric patients were enrolled in to this.. double-blinded study."	Quote: "..a "blinded" coinvestigator continuously monitored the patient's.." "PACU staff was unaware of patient enrolment."	Quote: "Because of the need to perform an open transvesical prostatectomy, one patient in Group 0.5mg was excluded." Comment: this missing is judged to have no clinical impact.	Comment: all outcomes are reported as dictated by the study protocol as written in the Methods section.	Comment: no other sources of bias identified.

APPENDIX 2 | Risk of bias table – authors' judgement *(continued)*

Reference	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Greenwood BK et al.[23]	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Unclear risk
Support for judgement	Quote: "..the patients were randomly allocated to one of the three groups." Comment: insufficient information about the sequence generation process.	Comment: not reported how allocation concealment was achieved.	Quote: "A double-blind, between-patient trial was designed.." "All patients received a similar soft gelatin capsule.."	Comment: not reported whether blinding outcome assessment was achieved.	Comment: no missing outcome data.	Comment: all outcomes are reported as dictated by the study protocol as written in the Methods section.	Comment: no other sources of bias identified.
Hargreaves J et al.[24]	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Unclear risk
Support for judgement	Quote: "The author wishes to thank Rocke Products for supplying the double-blind randomized premedication.." Comment: not reported whether random sequence generation was achieved.	Comment: not reported how allocation concealment was achieved.	Quote: "Ninety patients..were allocated to three groups in a double-blind study" "This comprised an active and a dummy preparation for the two study groups and tow dummy preparation for the placebo group.	Comment: not reported whether blinding outcome assessment was achieved.	Comment: no missing outcome data.	Comment: all outcomes are reported as dictated by the study protocol as written in the Methods section.	Comment: no other sources of bias identified.

APPENDIX 2 | Risk of bias table – authors' judgement *(continued)*

Reference	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Kain ZN et al.[25]	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Unclear risk
Support for judgement	Quote: "Randomization was performed according to a computer-generated list created from a random numbers table."	Quote: "Blinding an randomization were handled by Yale-New Haven Hospital's investigational pharmacy,.." Comment: central allocation.	Quote: "Blinding an randomization were handled by Yale-New Haven Hospital's investigational pharmacy, an no other individuals (e.g. anesthesiologists, surgeons, investigators) were informed of the particular treatment group of which a particular subject was assigned." "Subjects received the intervention, midazolam or saline from coded syringes.." Comment: Likely that patients were blinded too.	Quote: "..no other individuals (e.g. anesthesiologists, surgeons, investigators) were informed of the particular treatment group of which a particular subject was assigned."	Quote: "Six subjects were excluded from the final sample because of noncompliance of the anesthesia staff to the study protocol. These subjects were excluded on the day of surgery, and no data were obtained regarding their postoperative course." Comment: unclear to which treatment group these patients belong; unbalancedness likely. Furthermore, no specific reasons for exclusion provided.	Comment: all outcomes are reported as dictated by the study protocol as written in the Methods section.	Comment: no other sources of bias identified.

APPENDIX 2 | Risk of bias table – authors' judgement *(continued)*

Reference	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Loach A et al.[26]	Low risk	High risk	Low risk	Unclear risk	Low risk	Low risk	Unclear risk
Support for judgement	Quote: "The allocation was made on the basis of numbers from random tables.."	Quote: "The allocation was made on the basis of numbers from random tables, and the code held by the Ward Sister." Comment: Although the code was held by the Ward Sister, it is unclear who enrolled the patients in the study. Furthermore, it is likely that no appropriate safeguards are taken.	Quote: "A randomised double blind trial was carried out.." "..patients then received two tablets which were either placebo or lorazepam.."	Comment: not reported whether blinding outcome assessment was achieved.	Comment: no missing outcome data on the outcome of interest for this review. From two patients, however, blood samples could not be obtained and these patients were missing on some other outcomes.	Comment: all outcomes are reported as dictated by the study protocol as written in the Methods section.	Comment: no other sources of bias identified.

APPENDIX 2 | Risk of bias table – authors' judgement *(continued)*

Reference	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Mijderwijk H et al.[7]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Support for judgement	Quote: "Randomisation was done by a computer-generated table."	Quote: "Randomisation was done by a computer-generated table, and patients were assigned subsequent numbers upon inclusion. Nurses who were not further involved in the care of these patients prepared the study medication according to the randomisation table." Comment: central allocation.	Quote: "The study was double blinded; the researchers, patients and all healthcare professionals involved in patient care were blinded to the treatment allocation.""Blinding was achieved by preparation of the transparent fluids in identical syringes."	Comment: as 'blinding of participants and personnel.'	Quote: "An Intention-to-treat analysis was applied.""14 patients from the lorazepam group and six patients from the NaCl 0.9% group were lost to follow-up for at least one of the measurement points. This difference was not significant." Comment: reasons for lost-to -follow up clearly described; no imbalancedness detected.	Comment: all outcomes are reported as dictated by the study protocol as written in the Methods section.	Comment: no other sources of bias identified.

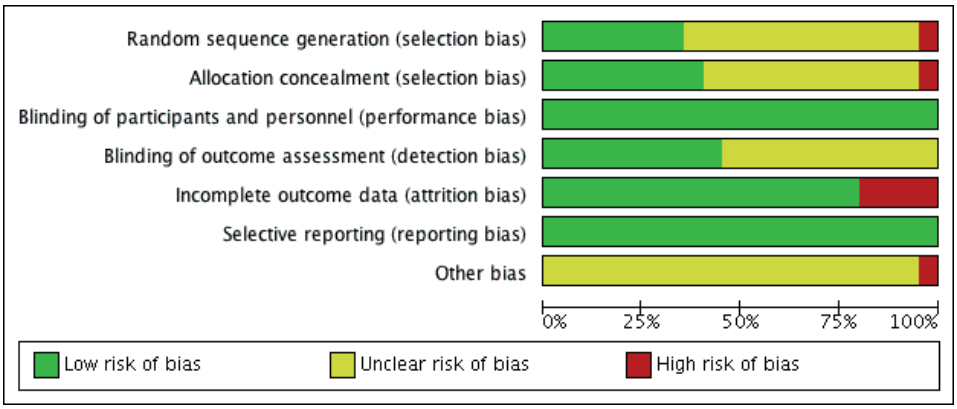
APPENDIX 2 | Risk of bias table – authors' judgement *(continued)*

Reference	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Oxorn DC et al.[27]	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Support for judgement	Quote: "On enrolment, patients were randomly allocated.." Comment: insufficient information about the sequence generation process.	Quote: "Sixty sealed envelopes were prepared."	Quote: "A syringe labelled study drug was prepared on the day of surgery by an anesthesiologist not involved with the conduct of the anesthetic. The anesthesiologist administering anesthesia was blinded to the patients group."	Quote: "The patient's responses were assessed by the same nurse who was blind tot the patient's treatment group."	Comment: no missing outcome data for our outcomes of interest. Furthermore, 4 missing data detected which was balanced over the treatment groups.	Comment: all outcomes are reported as dictated by the study protocol as written in the Methods section.	Comment: no other sources of bias identified.
Raeder JC et al.[28]	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Support for judgement	Quote: "The patients were then randomly allocated to one of the three groups" Comment: insufficient information about the sequence generation process.	Comment: not reported how allocation concealment was achieved.	Quote: "The patients did not know which premedicant they received. Mo-Scop or placebo were given double-blind from coded ampoules."	Comment: the outcome relevant for this review was based on patient's self-assessment. However, outcomes reported that were not relevant for this review were assessed by health care professionals. It remains unclear if those were blinded.	Comment: 186 of 193 patients did not complete postoperative questionnaire. Reasons for these missing data are not provided. However, these missings are judged to have no clinical impact.	Comment: all outcomes are reported as dictated by the study protocol as written in the Methods section.	Comment: no other sources of bias identified.

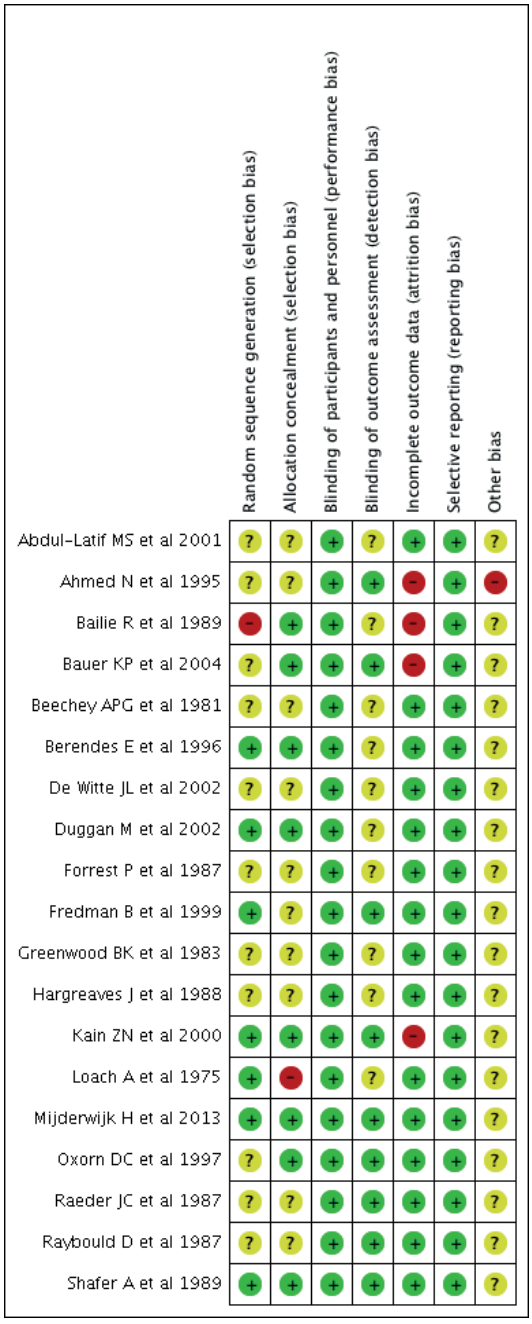
APPENDIX 2 | Risk of bias table – authors' judgement *(continued)*

Reference	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Raybould D et al.[29]	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Support for judgement	Quote: "..they were allocated at random to one of three groups." Comment: insufficient information about the sequence generation process.	Comment: not reported how allocation concealment was achieved.	Quote: "A double-blind, between-patient trial was designed.." "All patients received a gelatin capsule with up to 20ml of water.."	Quote: "The observer was trained, was the same throughout and was unaware of the medication given."	Quote: "Several patients had to be withdrawn from the study because of problems in the timing of operation or because more major surgery was indicated." Comment: 7 patients had to be withdrawn, which was judged to satisfactory balanced over the treatment groups (placebo versus active). This was judged to have no clinical impact.	Comment: all outcomes are reported as dictated by the study protocol as written in the Methods section.	Comment: no other sources of bias identified.
Shafer A et al.[30]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Support for judgement	Quote: "Patients were randomly assigned using a computer-generated random number list.."	Quote: "Only the pharmacist who prepared the study-drug vials knew to which group a patient was assigned." Comment: central allocation.	Quote: "Only the pharmacist who prepared the study-drug vials knew to which group a patient was assigned.""..all study drugs were administered in a double-blinded manner."	Quote: "A blinded observer noted the incidence of coughing,.. and assessed overall difficulties during the induction and maintenance phases of anesthesia." Comment: outcome relative to this review are assessed by patient's self-assessment.	Quote: "Overall, an 89% response rate was obtained on the follow-up questionnaires." Comment: Although no reasons for these missing are provided, these missings are judged to have no clinical impact.	Comment: all outcomes are reported as dictated by the study protocol as written in the Methods section.	Comment: no other sources of bias identified.

APPENDIX 3 | Summary risk of bias graph



APPENDIX 4 | Individual risk of bias score



APPENDIX 5 | Meta-regression

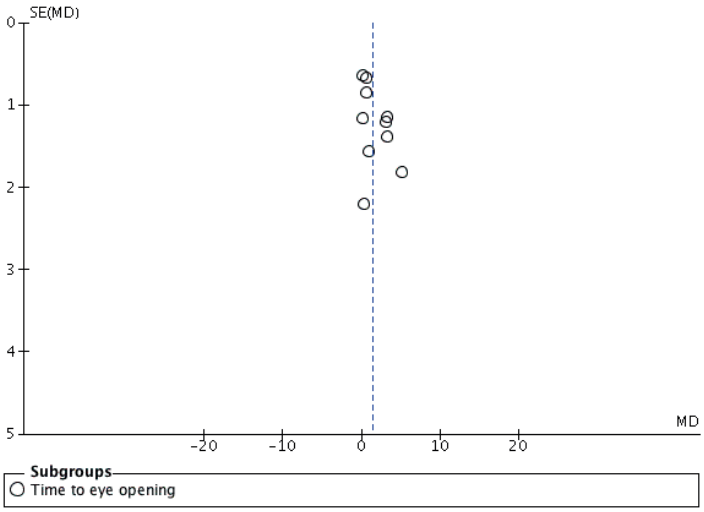
Covariate	b	95% CI	
		Lower bound	Upper bound
Time to recovery			
Time to eye opening			
Year of publication	-0.11	-0.28	0.06
Methodological quality	0.64	-0.08	1.36
Impact factor	-0.19	-1.16	0.77
TCR			
Year of publication	-0.19	-0.75	0.37
Methodological quality	1.68	0.53	2.83
Impact factor	0.46	-3.30	4.22
Time to early recovery			
Year of publication	0.37	-1.81	2.55
Methodological quality	-1.27	-9.37	6.83
Impact factor	-2.56	-12.66	7.54
Time to discharge			
Year of publication	0.28	-0.85	1.42
Methodological quality	0.19	-11.91	12.29
Impact factor	-0.18	-3.06	2.70
Postoperative side effects			
Headache			
Year of publication	0.08	-0.31	0.47
Methodological quality	-0.86	-2.61	0.89
Impact factor	-0.50	-1.12	0.11
Nausea			
Year of publication	-0.00	-0.05	0.05
Methodological quality	-0.17	-0.58	0.25
Impact factor	0.20	-0.02	0.42
Vomiting			
Year of publication	0.01	-0.08	0.09
Methodological quality	0.32	-0.15	0.80
Impact factor	-0.17	-0.82	0.49
Dizziness			
Year of publication	-0.16	-0.49	0.16
Methodological quality	0.20	-1.31	1.71
Impact factor	-0.47	-2.28	1.33
Pain			
Year of publication	NA	NA	NA

APPENDIX 5 | Meta-regression *(continued)*

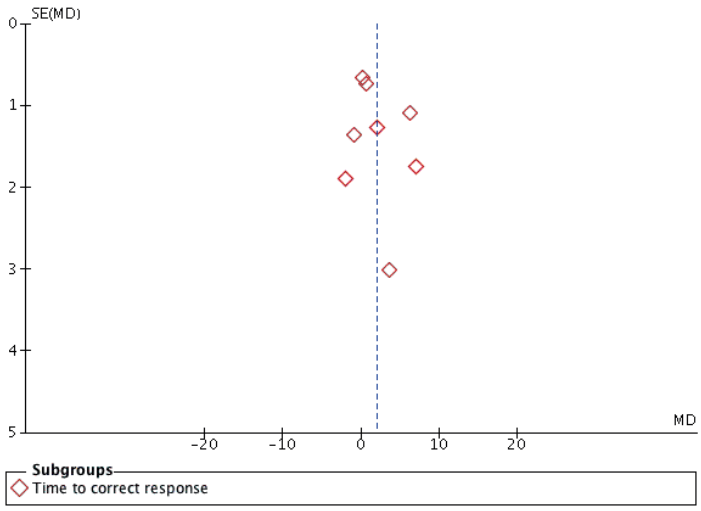
Covariate	b	95% CI	
		Lower bound	Upper bound
Methodological quality	NA	NA	NA
Impact factor	NA	NA	NA
Miscellaneous			
Year of publication	NA	NA	NA
Methodological quality	NA	NA	NA
Impact factor	NA	NA	NA
Psychological outcome			
Anxiety			
Year of publication	0.12	-0.26	0.50
Methodological quality	-1.01	-6.33	-4.32
Impact factor	-0.20	-3.57	3.18

B=regression coefficient; CI=confidence interval; TCR=time to first correct response; NA=not applicable.

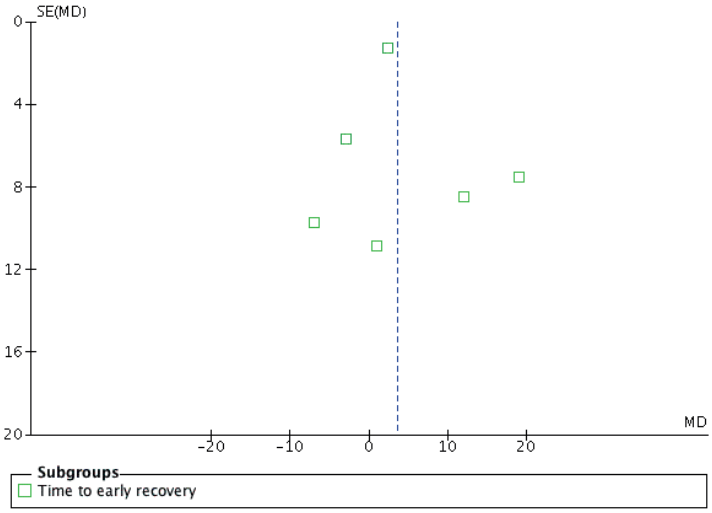
APPENDIX 6A | Funnel plots for time to recovery (time to eye opening)



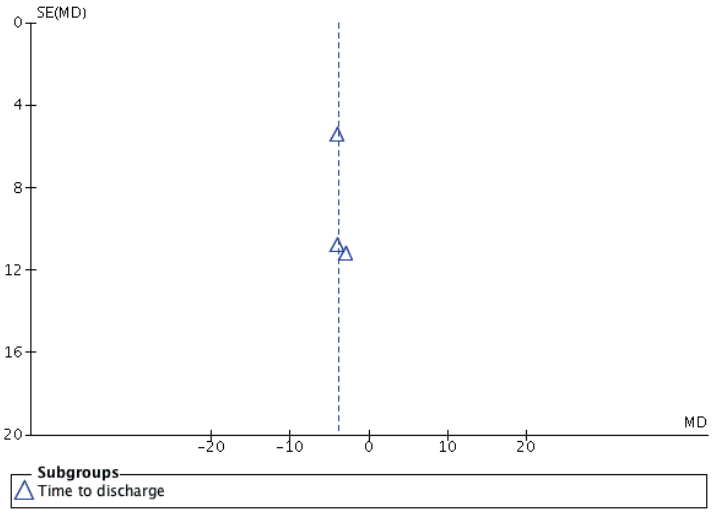
APPENDIX 6A | Funnel plots for time to recovery (time to first correct response)



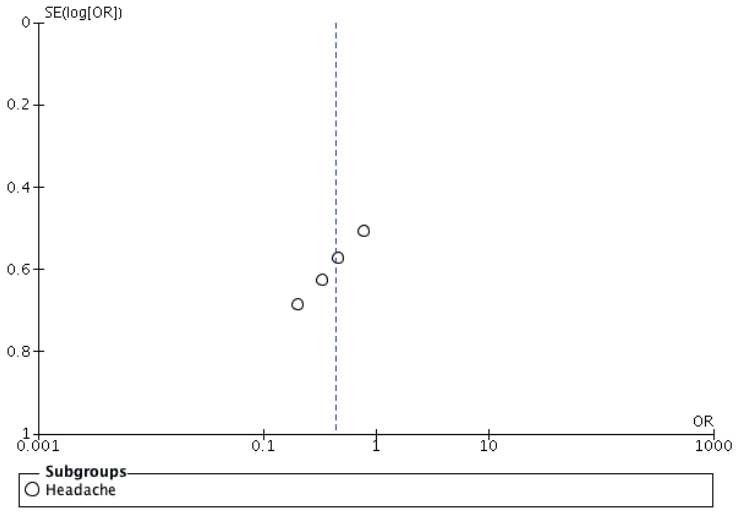
APPENDIX 6A | Funnel plots for time to recovery (time to early recovery)



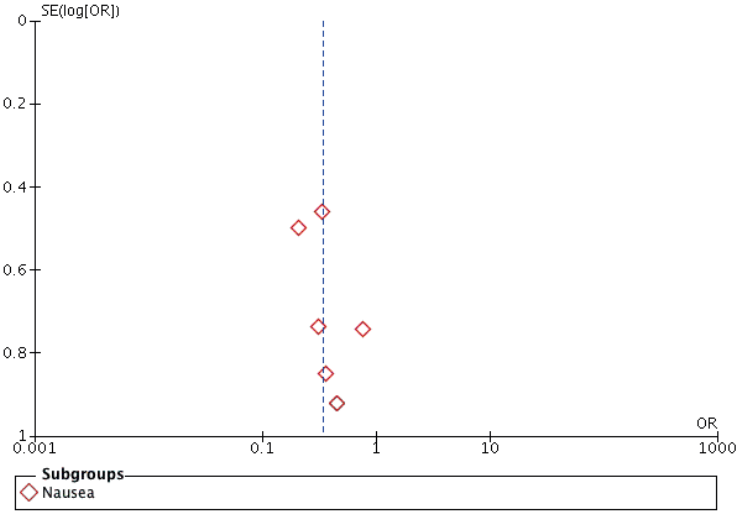
APPENDIX 6A | Funnel plots for time to recovery (time to discharge)



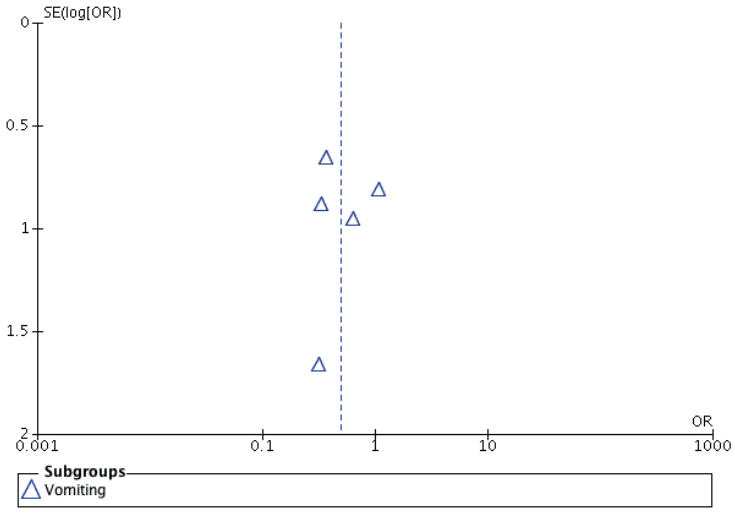
APPENDIX 6B | Funnel plots for postoperative side effects (headache)



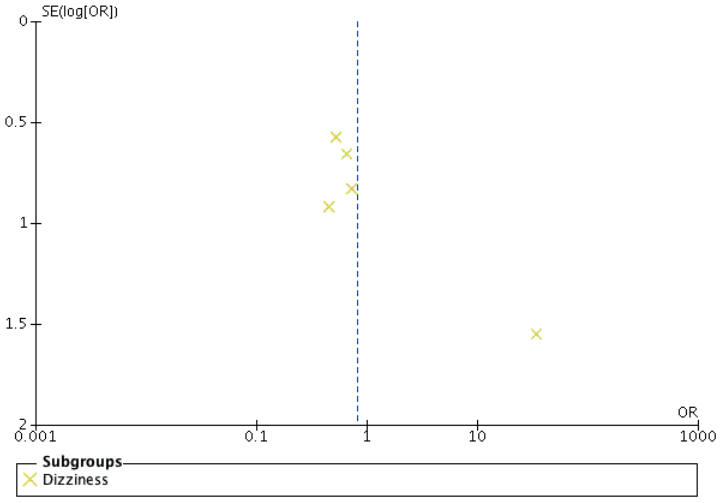
APPENDIX 6B | Funnel plots for postoperative side effects (nausea)



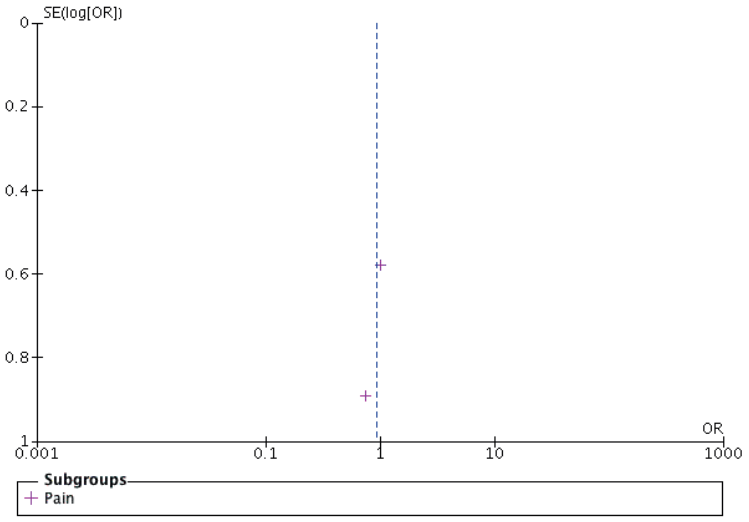
APPENDIX 6B | Funnel plots for postoperative side effects (vomiting)



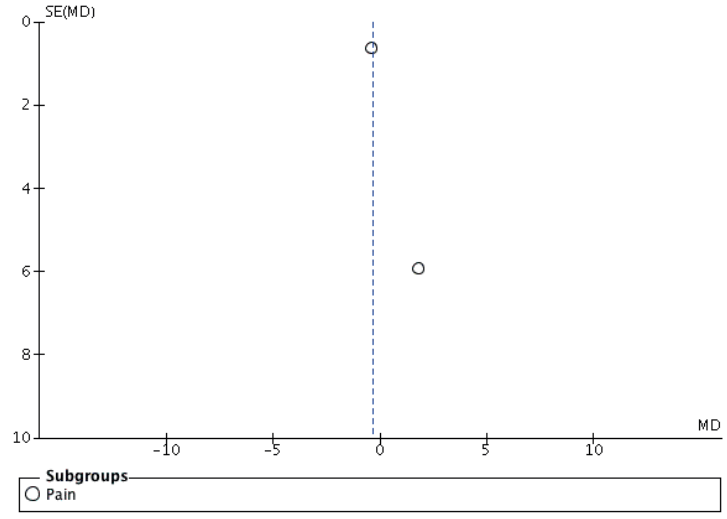
APPENDIX 6B | Funnel plots for postoperative side effects (dizziness)



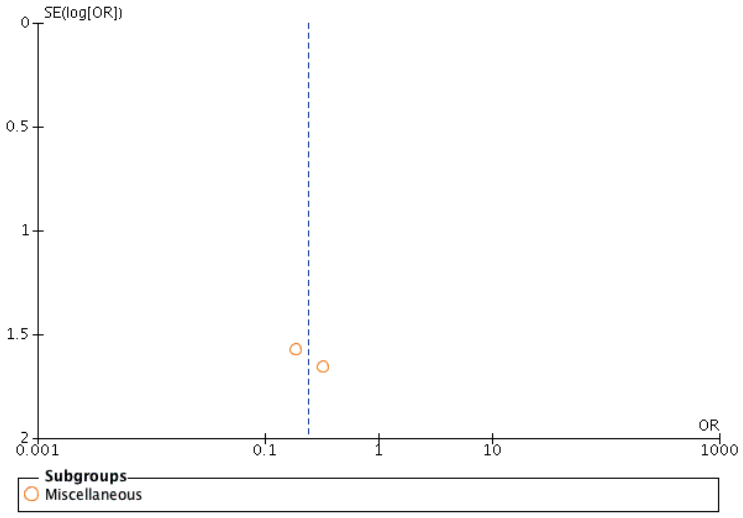
APPENDIX 6B | Funnel plots for postoperative side effects (pain)



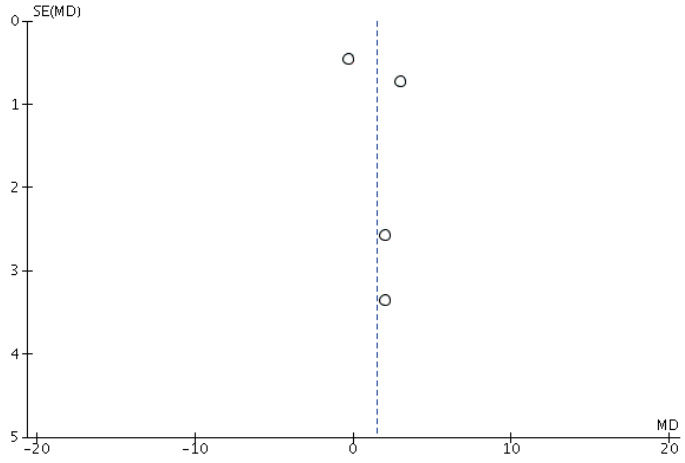
APPENDIX 6B | Funnel plots for postoperative side effects (pain, continuous)



APPENDIX 6B | Funnel plots for postoperative side effects (miscellaneous)



APPENDIX 6C | Funnel plots for psychological phenomena (anxiety)



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IDENTIFYING VULNERABLE PATIENTS

PART 2


CF
BZD
R^2

PROGNOSTIC MODEL FOR PSYCHOLOGICAL OUTCOME IN DAY-CASE SURGERY PATIENTS: A PROSPECTIVE STUDY USING A STRUCTURAL EQUATION MODELING FRAMEWORK

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Ewout W. Steyerberg

CHAPTER 5

Submitted

ABSTRACT

Surgical procedures are increasingly carried out in a day-case setting. Along with this increase, psychological outcomes have become prominent. The objective was to evaluate the prognostic effects of sociodemographic, medical, and psychological variables assessed before day-case surgery on psychological outcomes after surgery in a prospective study. The study was carried out between October 2010 and September 2011. We analyzed 398 mixed patients, from a RCT, undergoing day-case surgery at a university medical center. Structural Equation Modeling was used to jointly study candidate prognostic variables relating to sociodemographics (age, gender, nationality, marital status, having children, religion, educational level, employment), medical status (BMI, heart rate), and psychological status (anxiety, fatigue, aggression, depression, self-esteem, self-efficacy), all assessed before surgery. We studied psychological outcomes on the seventh day after surgery, including anxiety (STAI-State/Trait, HADS-A), fatigue (MFI), depressive moods (HADS-D) and aggression regulation (STAS-State/Trait). The final prognostic model comprised the following prognostic variables: anxiety (STAI-State/Trait, HADS-A), fatigue (MFI), depression (HADS-D), aggression (STAS-State/Trait), self-efficacy, gender and having children. The corresponding psychological variables as assessed at baseline were prominent – i.e. standardized regression coefficients ≥ 0.20 –, with the score on STAI-Trait being the strongest predictor overall. STAI-State (adjusted $R^2 = 0.44$), STAI-Trait (0.66), HADS-A (0.45) and STAS-Trait (0.54) were best predicted. We provide a prognostic model that adequately predicts multiple outcomes in day-case surgery. Consequently, timely identification of vulnerable patients who may require additional medical or psychological preventive treatment becomes feasible.

INTRODUCTION

Surgical procedures are increasingly carried out in a day-case setting.[1,2] The patients' perception of perioperative health in day-case surgery is currently not dominated by medical factors but by psychological factors[3,4] including anxiety, depressive moods, aggression and feelings of fatigue.[5] This shift calls for new research that provides prediction of these clinical outcomes to aid early clinical decision making, a task that, particularly, belongs to anesthesiologists' preoperative assessment.[6]

Prognostic models are statistical models that combine data from patients to predict clinical outcome.[7] Such models based on data collected soon after presentation could in theory be used to aid early clinical decision making and allow more accurate counseling of patients.[7] Conventionally, prognostic studies aim to find prognostic factors that accurately predict a single outcome variable.[8] However, joint prediction of interrelated outcome variables, such as psychological outcome variables, has not yet been studied extensively. To that end, advanced statistical methodology like Structural Equation Modeling (SEM) is needed. SEM enables joint analyzes of several candidate prognostic factors on several outcome variables.[9] SEM has been used in many research fields and is currently emerging in clinical medicine.[10] However, in the field of anesthesiology it has been rarely used, although it was previously mentioned that this statistical methodology should be further established.[11]

We aimed to develop a prognostic model based on sociodemographic, medical, and psychological variables assessed just before day-case surgery on psychological outcomes after surgery using SEM.

METHODS

Study population and study design

This study is part of a larger double-blinded randomized controlled clinical trial, conducted at the Erasmus University Medical Center, comparing the effects of lorazepam and placebo in day-case surgery patients.[5] However, the methods in this study have been adapted to address different objectives. We recruited patients from our day-case surgery department between October 2010 and September 2011. We included all patients who were referred for day-case surgery and aged at least 18 years. Patients were excluded if they met one or more of the following criteria: insufficient command of the Dutch language; severe learning difficulties; or undergoing ophthalmology surgery, extracorporeal shock wave lithotripsy

(ESWL), endoscopy, Botox treatment, abortion, or chronic pain treatment. The latter procedures are generally considered to be minimally invasive. Most practitioners are of the opinion that these procedures do not require premedication. Finally, prior use of psychopharmaceuticals and contraindication to lorazepam use – according to our national pharmacotherapeutic compass – were also exclusion criteria. The study protocol was approved by the Medical Ethical Committee of Erasmus MC (Chairperson Prof. dr. H.W. Tilanus) and by the Netherlands Central Committee on Research involving Human Subjects (CCMO) and registered with EudraCT under number 2010-020332-19. The trial has also been registered under identification number NCT01441843 in the ClinicalTrials.gov protocol registration system. Written informed consent was obtained from all subjects. The time schedule for the current study is shown in Figure 1.

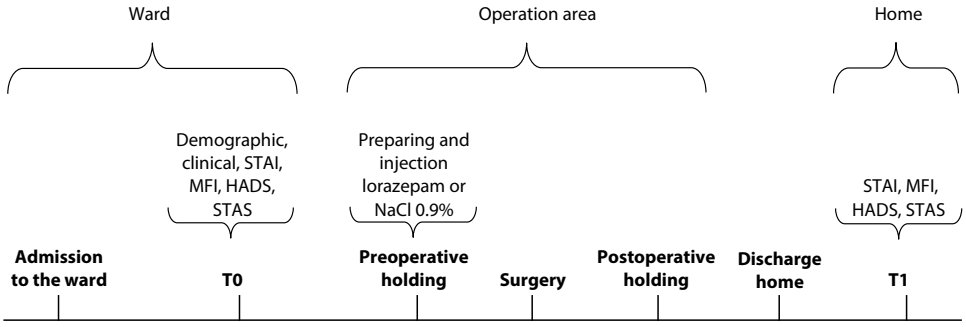

FIGURE 1 | Timeline of the study

T0 = baseline assessment on the day of surgery (self-reported questionnaire); T1 = seventh postoperative day (self-reported questionnaire); STAI, State-Trait Anxiety Inventory; MFI, Multidimensional Fatigue Inventory; HADS, Hospital Anxiety and Depression Scale, STAS: State-Trait Anger Scale.

Outcome variables

State-Trait Anxiety Inventory (STAI)

Anxiety was measured using the Dutch version of the STAI.[12] The STAI consists of two 20-item scales. One scale measures how one feels in general (Trait anxiety), while the other measures how one feels at the present moment (State anxiety). All items are rated on a 4-point Likert scale, ranging from 1 ("not at all") to 4 ("all the time"). Sum scores for both scales were calculated by adding the scores of all the items, theoretically ranging from 20 to 80. A higher score indicates a higher level of anxiety. STAI has been shown to have good validity, and the STAI-State and STAI-Trait scales have similar reliability scores: Cronbach's $\alpha > 0.80$.[12]

Multidimensional Fatigue Inventory (MFI)

Fatigue was measured using the Dutch version of the MFI,[13] a 20-item questionnaire covering five scales: General fatigue, Physical fatigue, Mental fatigue, Reduced motivation, and Reduced activity. Each scale has four items and each item is rated on a 5-point Likert scale, ranging from one ("yes, that is true") to five ("no, that is not true"). A sum score was calculated by adding the scores of all the items, theoretically ranging from 20 to 100. A higher score indicates a higher degree of fatigue. In the majority of cases, MFI has good validity and reliability, with Cronbach's α exceeding 0.80.[13]

Hospital Anxiety and Depression Scale (HADS)

Depressive moods were measured using a Dutch version of the HADS,[14] which consists of two 7-item scales: one for anxiety (HADS-A) and one for depression (HADS-D). Each item comprises four answer alternatives and for each of the scales the total score theoretically ranges from 0 to 21. A higher score indicates a higher degree of either anxiety or depression. The HADS is known to have adequate validity and internal consistency in the Dutch population (Cronbach's α = 0.88[15]).

State-Trait Anger Scale (STAS)

Aggression regulation was assessed using the Dutch version of the STAS,[16] which consists of two 10–item scales, one covering the State-aggression (how angry one feels at the moment) and one covering the Trait-aggression (how angry one feels in general). Each item is rated on a 4-point Likert scale, ranging from one ("not at all") to four ("all the time"). The theoretical scores range from 10 to 40. A higher score indicates a higher degree of aggression. Both subscales have adequate validity; the STAS-State has good reliability (Cronbach's α = 0.93), as does the STAS-Trait (Cronbach's α = 0.88).[16]

Sociodemographic and medical prognostic variables

The sociodemographic variables we considered were gender, age, educational level, marital status, employment, religion, having children, and type of nationality (i.e. Dutch versus non-Dutch). The medical variables we considered were Body Mass Index (BMI) and preoperative heart rate (HR).

Psychological prognostic variables

Baseline assessment of outcome variable

Baseline assessments of all psychological outcome variables were used as candidate prognostic variables.

Rosenberg Self-Esteem Scale (RSES)

Self-esteem was measured using the ten-item Dutch version of the RSES.[17] Each item was rated on a 4-point Likert scale from 1 ("strongly agree") to 4 ("strongly disagree"). The sum score theoretically ranges from 10 to 40. A higher score indicates a higher degree of self-esteem. RSES has good validity and reliability with a Cronbach's α of 0.87.[17]

General Self-Efficacy Scale (GSES)

Self-efficacy was measured using the Dutch version of the GSES.[18] Each item is rated on a 4-point Likert scale. The scores of the ten items range from 1 ("not at all true") to 4 ("exactly true"). Consequently, the theoretical sum score ranges from 10 to 40. A higher score indicates a higher degree of self-efficacy. Besides an adequate validity, GSES has a reliability of 0.85 (Cronbach's α) in the Dutch population.[19]

Statistical analysis

We explored the relations between baseline assessments (T0, just before surgery) and outcome variables (T1, seventh day after surgery). We included sociodemographic, medical and psychological variables assessed at baseline in the model simultaneously. Predictor variables were entered for all outcomes in the model to allow for insight in the relative importance of each predictor. The analyses were guided by statistical and clinical-theoretical criteria. The first step was to analyze all predictor variables together with the seven outcome variables that were assessed on the seventh day after surgery. In the second step, we eliminated less-relevant predictor variables according to the backward elimination procedure (*P*-to-remove > 0.20 on at least four outcome variables) provided that there is no substantial loss of information (i.e. a decrease in *P*-value for model fit ≥ 0.10). Type of intervention as randomized was adjusted for.

Modeling was performed using the Maximum Likelihood (ML) as estimation method. As the distributions of the variables were considered non-normal, the final modeling was performed using the Maximum Likelihood for Robustness (MLR) as estimation method.

The following measures were used to test for adequacy of the model fit:
1. Chi-square for model fit (low and non-significant values of the chi-square are desired; *P*-value > 0.05); 2. Chi-square/degrees of freedom ratio (a value < 2.0 was considered to be acceptable); 3. Comparative Fit Index (CFI), and Tucker-Lewis Index (TLI) (high values are desired (> 0.95);[20,21] 4. Root Mean Square Error of Approximation (RMSEA: a value < 0.05 indicates a close fit);[22] and 5. Standardized Root Mean Squares of Residuals (SRMR: a value of < 0.08 indicates a reliable fit).[23] After testing for goodness-of-fit, it was of particular clinical interest to calculate the percentages of explained variance for each outcome variable.

There was little missing data (< 5% for all variables), which were not included in the prognostic analysis. Bootstrapping was used for internal validation.[24,25] Each subsample was a random sample with replacement from the full sample. We checked the internal validity of the prognostic model using 1000 bootstrap samples. Bias-corrected standard errors were estimated. For each predictor, we estimated the unstandardized regression coefficients, including the 95% bootstrapped confidence intervals, and standardized regression coefficients as effect estimates.

We used SPSS version 20.0 (IBM Corp. Armonk, NY) and Mplus version 7 (Muthén and Muthén, Los Angeles, CA) for statistical analyzes. Estimates were regarded statistically significant if the two-sided *P*-value was < 0.05.

RESULTS

We included 398 patients, who all completed measurement at baseline, while 383 (96%) completed measurement at follow-up. The study population had more males (56%) than females and most of the patients were Dutch (94%). The majority (60%) lived together with a partner, and approximately half of the patients had children. About two-thirds reported being non-religious. 270 patients (68%) had a middle level of education, whereas lower but similar numbers of patients had low ($n = 63$) and high ($n = 65$) levels of education. Three-quarters of the patients were employed. The median age was 36.7 years, the median BMI ((body weight in kilograms)/(body height in meters)^2) was 24.6, and the median preoperative HR (beats per minute) was 69 (Table 1).

Mean anxiety scores (STAI-State, STAI-Trait and HADS-A) decreased after surgery, whereas the mean values for aggression scores (STAS-State and STAS-Trait) and depression scores (HADS-D) remained about the same over time (Table 2). Mean fatigue scores (MFI) increased postoperatively.

TABLE 1 | General characteristics of the patients at baseline

Categorical	*n*	%
Type of intervention		
Verum (lorazepam)	198	49.7
Placebo (NaCl 0.9%)	200	50.3
Gender		
Female	174	43.7
Male	224	56.3
Nationality		
Dutch	374	94.0
Non-Dutch	24	6.0
Marital Status[a]		
Single	158	39.7
Together	240	60.3
Children		
Yes	206	51.8
No	192	48.2
Religion		
Yes	128	32.2
No	270	67.8
Educational level[b]		
Low	63	15.8
Middle-level	270	67.8
High	65	16.3
Employment		
Yes	301	75.6
No	97	24.4

Continuous		Percentiles		
	n	25	50	75
Age	398	28.8	36.7	49.4
BMI[c]	398	22.4	24.6	27.7
Heart rate[d]	396	62.0	69.0	78.0

[a] Single: unmarried, divorced, widow(er); Together: married, living together; [b] Low: no education, elementary school, preparatory middle-level vocational education; Middle-level: middle-level vocational education, higher general continued education, higher vocational education; High: preparatory university education, university education; [c] Body Mass Index: body weight in kilogram)/(body height in meters)^2; [d] Heart rate: beats per minute.

TABLE 2 | Descriptive of psychological variables

	Baseline (T0)		7th day after surgery (T1)	
	mean	SD	mean	SD
STAI-State	38.1	9.4	30.3	8.9
STAI-Trait	33.5	8.1	30.5	8.7
HADS-A	4.7	3.1	2.9	2.9
MFI	41.6	13.1	48.5	17.0
STAS-State	10.2	1.2	10.6	2.5
STAS-Trait	13.4	3.6	13.1	3.6
HADS-D	3.0	2.4	2.8	2.9
RSES	33.5	4.4	NA	NA
GSES	31.6	4.2	NA	NA

Abbreviations: STAI-State, State-Trait Anxiety Inventory, State part; STAI-Trait, State-Trait Anxiety Inventory, Trait part; MFI, Multidimensional Fatigue Inventory; HADS-A, Hospital Anxiety and Depression Scale, Anxiety part; HADS-D, Hospital Anxiety and Depression Scale, Depression part; STAS-State, State-Trait Anger Scale, State part; STAS-Trait, State-Trait Anger Scale, Trait part; RSES, Rosenberg Self-Esteem Scale; GSES, General Self-Efficacy Scale; NA = not applicable. T0: *n* = 398; T1: *n* = 383.

Correlations between prognostic variables and outcomes over time

At T0 (baseline), the highest correlations were found between HADS-A and STAI-Trait (r = 0.66), and HADS-A and STAI-State (r = 0.66, Table 3). Also, STAI-Trait correlated substantially with STAI-State (r = 0.52), MFI (r = 0.54) and HADS-D (r = 0.55). At T1 (seventh day after surgery), the intercorrelations were substantial. The highest correlations were found between STAI-State and STAI-Trait (r = 0.76) and between STAI-State and HADS-A (r = 0.71). STAI-Trait had a correlation of 0.71 with HADS-A. The intracorrelations over time of most of the psychological outcome variables varied from moderate to substantial: STAI-State (r = 0.42), STAI-Trait (r = 0.79), HADS-A (r = 0.59), MFI (r = 0.54), STAS-Trait (r = 0.68) and HADS-D (r = 0.55). STAS-State showed a correlation of only 0.16, however (Table 3).

Prognostic potentialities of baseline variables

The final model comprised the following predictors: gender, having children, STAI-State, STAI-Trait, HADS-A, MFI, STAS-State, STAS-Trait, HADS-D and GSES. Nationality, marital status, religion, educational level, employment, age, BMI, HR, RSES and type of intervention as randomized were fixed at zero. The performance measures all showed adequate values: using the MLR as the estimation method, the *P*-value for the chi-square for model fit (98.99; df = 77) turned out to be just significant (*P* = 0.05), while

TABLE 3 | Correlation matrix of baseline and outcome variables according to the final prognostic model

			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
	Baseline predictors (T0)																		
1	Gender																		
2	Children		-0.03																
3	Anxiety	STAI-State	0.27	-0.03															
4		STAI-Trait	0.16	-0.07	0.52														
5		HADS-A	0.18	-0.05	0.66	0.66													
6	Fatigue	MFI	0.12	-0.07	0.38	0.54	0.42												
7	Aggression	STAS-State	-0.02	-0.08	0.13	0.15	0.11	0.02											
8		STAS-Trait	0.05	-0.05	0.15	0.47	0.27	0.23	0.25										
9	Depression	HADS-D	-0.02	0.05	0.35	0.55	0.48	0.49	0.00	0.20									
10	Self-Efficacy	GSES	-0.16	0.09	-0.24	-0.32	-0.28	-0.27	0.08	-0.10	-0.23								
	Outcomes (T1)																		
11	Anxiety	STAI-State	0.11	0.04	0.42	0.61	0.51	0.51	0.13	0.28	0.46	-0.14							
12		STAI-Trait	0.12	-0.03	0.45	0.79	0.63	0.52	0.16	0.43	0.55	-0.27	0.76						
13		HADS-A	0.06	-0.02	0.35	0.59	0.59	0.40	0.14	0.30	0.47	-0.14	0.71	0.71					
14	Fatigue	MFI	0.17	0.03	0.29	0.34	0.31	0.54	0.04	0.16	0.30	-0.11	0.58	0.45	0.46				
15	Aggression	STAS-State	0.07	0.07	0.15	0.34	0.31	0.21	0.16	0.26	0.18	-0.08	0.51	0.44	0.52	0.30			
16		STAS-Trait	0.13	0.00	0.25	0.54	0.41	0.25	0.09	0.68	0.25	-0.15	0.45	0.56	0.54	0.26	0.54		
17	Depression	HADS-D	0.04	0.09	0.26	0.52	0.36	0.43	0.09	0.28	0.55	-0.16	0.66	0.60	0.63	0.57	0.45	0.40	

Abbreviations: STAI-State, State-Trait Anxiety Inventory, State part; STAI-Trait, State-Trait Anxiety Inventory, Trait part; MFI, Multidimensional Fatigue Inventory; HADS-A, Hospital Anxiety and Depression Scale, Anxiety part; HADS-D, Hospital Anxiety and Depression Scale, Depression part; STAS-State, State-Trait Anger Scale, State part; STAS-Trait, State-Trait Anger Scale, Trait part; GSES, General Self-Efficacy Scale.
Significant values (P <0.05; two-tailed) are represented in bold face; Gender: 0 = male, 1 = female; Children: 0 = no children, 1 = having children; T1 = 7th day after surgery.
Gray: intracorrelations of psychological variables.

TABLE 4 | Prognostic performance of the baseline variables in the final model: explained variances

		R^2 Adjusted		
		A	B	C
Outcome variables				
Anxiety	STAI-State	0.01	0.01	0.44
	STAI-Trait	0.01	0.01	0.66
	HADS-A	0.00	0.00	0.45
Fatigue	MFI	0.02	0.02	0.31
Aggression	STAS-State	0.01	0.01	0.15
	STAS-Trait	0.01	0.01	0.54
Depression	HADS-D	0.00	0.00	0.38

Abbreviations: STAI-State, State-Trait Anxiety Inventory, State part; STAI-Trait, State-Trait Anxiety Inventory, Trait part; MFI, Multidimensional Fatigue Inventory; HADS-A, Hospital Anxiety and Depression Scale, Anxiety part; HADS-D, Hospital Anxiety and Depression Scale, Depression part; STAS-State, State-Trait Anger Scale, State part; STAS-Trait, State-Trait Anger Scale, Trait part; GSES, General Self-Efficacy Scale.

A = Demographic variables assessed at baseline

B = Demographic and Medical variables assessed at baseline

C = Demographic, Medical, Psychological variables assessed at baseline

TABLE 5 | Individual estimates of the final prognostic model

		Anxiety (STAI-State)				Anxiety (STAI-Trait)				Anxiety (HADS-A)			
		b[#]	95% CI$_b$		B[$]	b	95% CI$_b$		B	b	95% CI$_b$		B
Intercept		-4.48	-12.90	5.11	NA	0.88	-5.66	8.22	NA	-5.41	-8.35	-2.23	NA
Gender		0.20	-1.22	1.50	0.01	0.00	-1.09	1.07	0.00	-0.12	-0.61	0.34	-0.02
Children		1.48	0.07	2.76	0.08	0.42	-0.63	1.44	0.02	0.09	-0.40	0.51	0.02
Anxiety	STAI-State	0.04	-0.06	0.14	0.05	-0.04	-0.12	0.04	-0.05	-0.04	-0.07	-0.01	-0.13
	STAI-Trait	0.40	0.22	0.55	0.36	0.56	0.44	0.67	0.52	0.10	-0.05	0.14	0.27
	HADS-A	0.34	-0.08	0.79	0.12	0.50	0.15	0.85	0.18	0.39	0.26	0.51	0.41
Fatigue	MFI	0.16	0.09	0.23	0.23	0.07	0.02	0.11	0.10	0.02	-0.01	0.04	0.08
Aggression	STAS-State	0.39	-0.57	0.77	0.05	0.35	-0.10	0.88	0.05	0.14	-0.12	0.31	0.06
	STAS-Trait	0.00	-0.26	0.25	0.00	0.20	0.03	0.41	0.08	0.03	-0.06	0.11	0.03
Depression	HADS-D	0.33	-0.09	0.78	0.09	0.46	0.16	0.78	0.13	0.17	0.03	0.31	0.14
Self-Efficacy	GSES	0.19	0.00	0.38	0.09	-0.01	-0.15	0.13	-0.01	0.06	0.00	0.11	0.08

TABLE 5 | Individual estimates of the final prognostic model *(continued)*

		Fatigue (MFI)				Aggression State (STAS-State)				Aggression Trait (STAS-Trait)				Depression (HADS-D)			
		b	95% CI_b		B	b	95% CI_b		B	b	95% CI_b		B	b	95% CI_b		B
Intercept		2.76	-15.91	22.83	NA	4.88	1.63	9.15	NA	4.10	0.58	8.12	NA	-5.14	-8.59	-1.75	NA
Gender		3.50	0.51	6.48	0.10	0.15	-0.21	0.61	0.03	0.36	-0.07	0.88	0.05	0.04	-0.43	0.52	0.01
Children		2.48	-0.55	5.20	0.07	0.56	0.18	1.11	0.11	0.35	-0.14	0.88	0.05	0.58	0.13	1.05	0.10
Anxiety	STAI-State	0.06	-0.16	0.26	0.04	-0.04	-0.07	-0.01	-0.14	-0.02	-0.05	0.02	-0.04	-0.01	-0.05	0.02	-0.04
	STAI-Trait	-0.02	-0.32	0.29	-0.01	0.06	0.00	0.13	0.19	0.11	0.05	0.19	0.25	0.09	0.04	0.15	0.26
	HADS-A	0.39	-0.42	1.07	0.07	0.19	0.04	0.37	0.24	0.19	0.05	0.37	0.16	-0.02	-0.13	0.11	-0.03
Fatigue	MFI	0.65	0.50	0.80	0.50	0.01	-0.01	0.04	0.07	-0.01	-0.04	0.01	-0.04	0.03	0.01	0.06	0.14
Aggression	STAS-State	0.23	-0.67	1.79	0.02	0.21	-0.15	0.44	0.11	-0.28	-0.62	-0.02	-0.10	0.12	-0.06	0.39	0.05
	STAS-Trait	0.07	-0.47	0.62	0.01	0.07	-0.02	0.20	0.10	0.58	0.48	0.68	0.57	0.05	-0.04	0.14	0.06
Depression	HADS-D	0.13	-0.70	0.86	0.02	-0.04	-0.20	0.09	-0.04	-0.06	-0.18	0.09	-0.04	0.43	0.28	0.59	0.36
Self-Efficacy	GSES	0.27	-0.15	0.65	0.07	0.01	-0.06	0.07	0.02	0.01	-0.06	0.08	0.02	0.02	-0.05	0.08	0.03

Abbreviations: STAI-State, State-Trait Anxiety Inventory, State part; STAI-Trait, State-Trait Anxiety Inventory, Trait part; MFI, Multidimensional Fatigue Inventory; HADS-A, Hospital Anxiety and Depression Scale, Anxiety part; HADS-D, Hospital Anxiety and Depression Scale, Depression part; STAS-State, State-Trait Anger Scale, State part; STAS-Trait, State-Trait Anger Scale, Trait part; GSES, General Self-Efficacy Scale; NA, not applicable.
[#]b = unstandardized regression estimate; [$]B = standardized regression estimate; CI_b = bootstrapped confidence interval for corresponding b; gender: 0 = male, 1 = female; Children: 0 = no children, 1 = having children. Used method: ML estimation.

the ML estimation method yielded a chi-square value of 97.36 (df = 77; $P = 0.06$). The chi-square/degrees of freedom ratio was 1.29. The comparative Fit Index (CFI) was 0.99, and Tucker-Lewis Index (TLI) 0.98. RMSEA was 0.03 (90% CI: 0.004 to 0.042). The SRMR was 0.02. The demographic variables had minor effects in the final model. Adding the medical variables did not affect the performance of the final model. In contrast, the prognostic potentialities of psychological baseline measurements were substantial. The adjusted explained variances (R^2 adjusted) ranged from 0.15 for State aggression (STAS-State) to 0.66 for Trait anxiety (STAI-Trait). STAI-State, HADS-A, MFI, STAS-Trait and HADS-D showed R^2 adjusted scores of 0.44, 0.45, 0.31, 0.54 and 0.38, respectively. In all, with the exception of aggression, the outcome variables were substantially predictable (Table 4).

For each outcome variable on the seventh day after surgery (T1) we considered the important prognostic variables according to the standardized estimates (B), as shown in Table 5. We focused on standardized estimates with a value of ≥ 0.20 only (Figure 2). For STAI-State, baseline STAI-Trait was the most important predictor (B = 0.36), followed by MFI (B = 0.23). In contrast, the baseline assessment of STAI-State had no high prognostic impact. For STAI-Trait, only baseline STAI-Trait was important (B = 0.52). For HADS-A, baseline HADS-A had the highest prognostic effect (B = 0.41), followed by STAI-Trait (B = 0.27). For MFI, only baseline MFI was of high prognostic relevance (B = 0.50). For STAS-State, HADS-A had substantial prognostic effect (B = 0.24). In contrast, the baseline assessment of STAS-State had no high prognostic impact. For STAS-Trait, baseline STAS-Trait dominated the prognostic variables (B = 0.57). STAI-Trait was also an important prognostic variable (B = 0.25). For HADS-D, two predictor variables were of prognostic importance: HADS-D (B = 0.36) and STAI-Trait (B = 0.26). The residuals of the outcomes were moderately interrelated (intercorrelations between 0.15 and 0.54).

DISCUSSION

We developed a prognostic model using sociodemographic, medical and psychological variables assessed just before day-case surgery that predicts multiple psychological outcomes after day-case surgery. Overall, apart from state aggression, the psychological outcome variables could be adequately predicted using the identified prognostic model. Sociodemographic and medical variables were of minor importance, with the exception of gender and having children. In contrast, the psychological variables as assessed at baseline were of prominent importance.

This model is of interest for improving patients' quality of recovery and is useful for preoperative decision making. Recently, prehabilitation programs have showed that

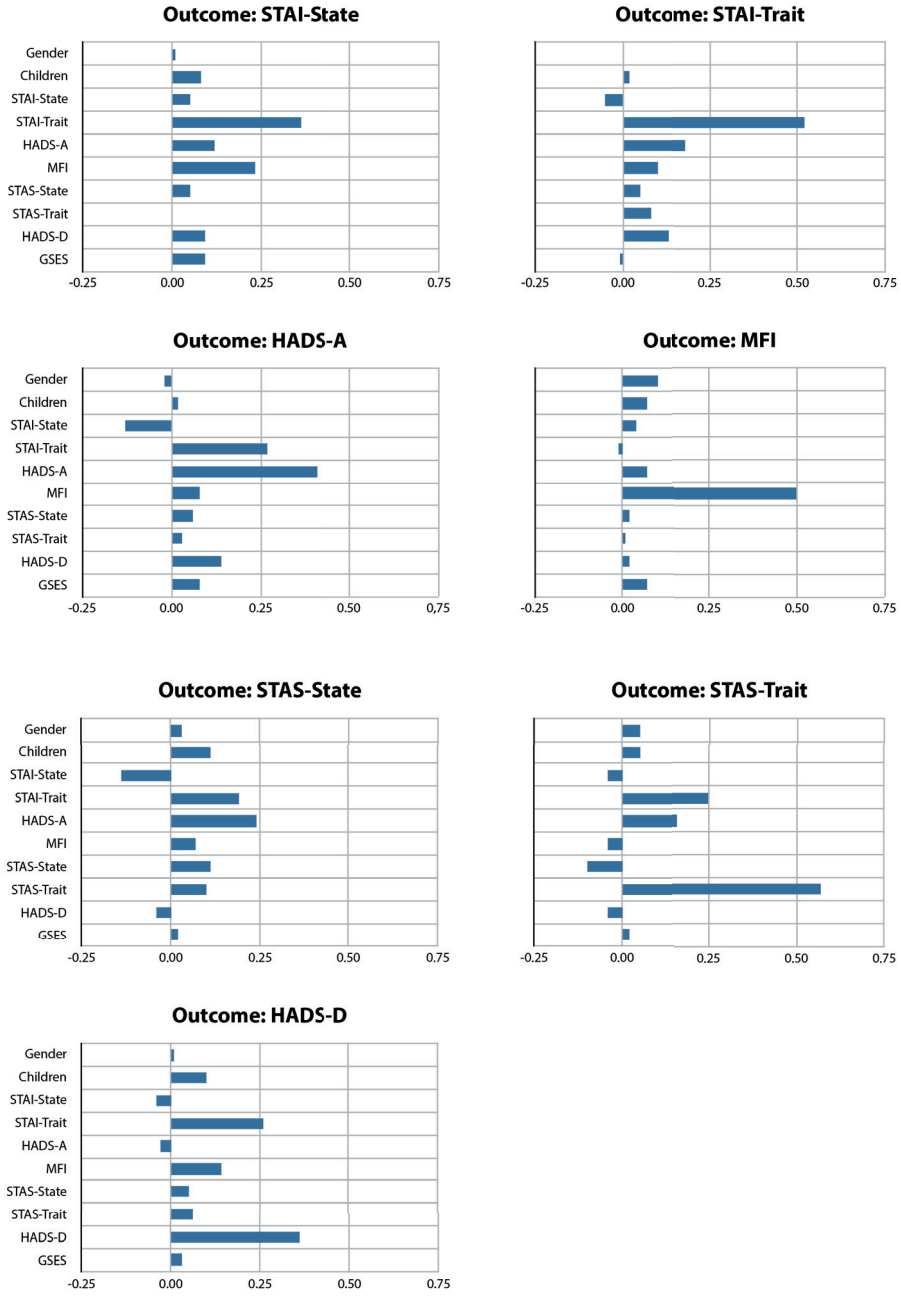

FIGURE 2 | Prognostic potentialities of the final predictor variables distinguished by outcome variables

optimal preoperative preparation leads to better postoperative outcomes.[26] These programs improve postoperative outcomes by using preoperative interventions. Prehabilitation programs may differ for different surgical populations,[27] and should be therefore tailored to the population of interest. One thing that should be developed in every single prehabilitation program is a preoperative prognostic model directed to vulnerable patients.[26] The provided preoperative prognostic model in this study enables predicting, simultaneously, multiple outcomes of interest in day-case surgery by means of only one prognostic model. Vulnerable patients can be identified and guided in adequate follow-up accordingly, which will lead to better postoperative outcomes together with reduction of negative socio-economic effects.

The model is also of interest for prognosis research dealing with psychological outcomes. First, from a clinical-theoretical perspective, the score on the STAI-Trait questionnaire showed to be a valuable prognostic variable for predicting almost all psychological outcome variables unless postoperative fatigue (B > 0.20). However, it was not powerful enough to replace the model. Sensitivity analysis that only included STAI-Trait as prognostic variable showed that only anxiety (STAI-State and STAI-Trait) as outcome variable was still adequately predicted, R^2 equalled 0.37 and 0.62 respectively. Concerning aggression and depression, the reduction in R^2 was considered too much, i.e. R^2 percentage reduction of > 20%. That STAI-Trait was not an important variable for predicting fatigue (R^2 < 0.20) is in line with earlier findings,[28] but understanding why postoperative fatigue does not follow the mechanisms of other psychological factors requires further study. Christensen et al. have suggested that the mechanisms cannot be explained by psychological factors.[29] However, more recently, it has been postulated that the underlying mechanism should be explained by psychological factors and mainly by its measurement itself.[28] Our results support the latter. Second, from a statistical modeling perspective, here we have applied structural equation modeling (SEM), a strong statistical approach, to evaluate the joint potentialities of several variables in predicting several outcomes. This joint analysis is especially preferred as psychological outcome variables are likely to interact with one another,[30] which is also observed in the present study. Next to this theoretical rationale of an integral analysis, SEM has a couple of additional advantages. SEM enables achieving a consistent set of predictors for all outcomes; and, accordingly, enables comparing the regression weights for the different outcome variables, which is difficult and time consuming when a conventional analysis was done (i.e. predicting each outcome individually). Furthermore, SEM tests if the prediction model represents adequately the data structure, with random fluctuation. Moreover, SEM gives insight in the related (residual) intercorrelations of the outcomes. When these residual intercorrelations would be high for some or all outcome variables

a principal component analysis or a partial least squares regression analysis would be indicated. This information would be missed in case of individual outcome analysis. It has to be noted that, ideally, a latent modeling approach seems indicated to analyze the joint prediction of observed variables. However, we have refrained from performing this approach as, in clinical practice, it is not plausible that the used measurements can be obtained without error.

Future considerations

Of the psychological outcomes analyzed, the explained variances (R^2) were substantially for the anxiety scales (STAI-State, STAI-Trait and HADS-A), the depression scale (HADS-D), the fatigue scale (MFI), and the trait component of aggression regulation (STAS-Trait). However, state aggression (STAS-State) was only moderately predictable. Although we found substantial explained variances as the criterion for assessing the performance of the individual outcomes in the current model, a number of variances still remain unexplained.

First, this could be due to the fallibility of the measurements. To assess such fallibility we evaluated the internal consistency of the measurements using Cronbach's α, both at baseline and 1 week after surgery. According to the commonly accepted criteria,[31] we concluded that internal consistency was satisfactory for all measurements (for the majority of the used scales Cronbach's $\alpha \geq .85$, four scales were in the range of 0.73 to 0.79), except for HADS-D assessed at baseline (Cronbach's $\alpha = 0.60$). In this study we used two different measurements for anxiety and found the interrelationships of STAI and HADS-A to be non perfect, in line with previous research.[32] This discrepancy suggests that the different instruments for anxiety have common and unique elements. Second, the model might be misspecified in principle, but we firmly believe that this possibility is not realistic. Third, the phenomenon of omitted variables may play a role in this study. Other unmeasured or as yet unknown variables may be of relevance, and consequently may, when added, enhance the prognostic performance of the model. While our study only comprises intrapersonal characteristics, interpersonal characteristics may also be important. For example, recent research has shown that negative dyadic coping (collaborative coping/dealing with stress within a couple) is associated with a higher degree of psychological distress.[33] Positive dyadic coping seems to be effective in dealing with problems surrounding illness, especially in older couples.[34] Such positive interpersonal variables could also help people cope in a perioperative setting. Environmental variables (e.g. living in suburbs), economic variables (e.g. economic crisis, being unemployed), and cultural variables could also be of interest. Adding such variables to our model may increase its prognostic performance.

Study limitations and study strengths

First, a limitation of this study was that the assessments were conducted at a single center, which means that further external validation is needed. Second, since we excluded patients who were taking psycho-pharmaceuticals and those with psychological disorders,[5] we can assume that the level of psychological dysfunction after day-case surgery could well be higher. This might bias our findings negatively, or strengthen our findings. Third, since the majority of our study population was Dutch, different results may be obtained when considering broader nationalities or ethnical and sociocultural groups.

Despite these limitations, the fact that our data were obtained in a RCT guarantees high quality of these data. Another strength of the study is the use of SEM. SEM appears to be a powerful approach that is suitable for conducting research on optimizing medical decision making using multiple outcome criteria.

CONCLUSION

We provide a prognostic model, using a structural equation modeling framework, that adequately predicts multiple outcomes in day-case surgery. This enables timely identification of vulnerable patients who may require additional medical or psychological preventive treatment.

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CLINICAL PREDICTION MODEL TO IDENTIFY VULNERABLE PATIENTS IN AMBULATORY SURGERY: TOWARDS OPTIMAL MEDICAL DECISION-MAKING

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CHAPTER 6

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ABSTRACT

Ambulatory surgery patients are at risk of adverse psychological outcomes such as anxiety, aggression, fatigue, and depression. We developed and validated a clinical prediction model to identify patients who were vulnerable to these psychological outcome parameters. We prospectively assessed 383 mixed ambulatory surgery patients for psychological vulnerability, defined as the presence of anxiety (state/trait), aggression (state/trait), fatigue, and depression seven days after surgery. Three psychological vulnerability categories were considered–i.e., none, one, or multiple poor scores, defined as a score exceeding one standard deviation above the mean for each single outcome according to normative data. The following determinants were assessed preoperatively: sociodemographic (age, sex, level of education, employment status, marital status, having children, religion, nationality), medical (heart rate and body mass index), and psychological variables (self-esteem and self-efficacy), in addition to anxiety, aggression, fatigue, and depression. A prediction model was constructed using ordinal polytomous logistic regression analysis, and bootstrapping was applied for internal validation. The ordinal *c*-index (ORC) quantified the discriminative ability of the model, in addition to measures for overall model performance (Nagelkerke's R^2). In this population, 137 (36%) patients were identified as being psychologically vulnerable after surgery for at least one of the psychological outcomes. The most parsimonious and optimal prediction model combined sociodemographic variables (level of education, having children, and nationality) with psychological variables (trait anxiety, state/trait aggression, fatigue, and depression). Model performance was promising: R^2 = 30% and ORC = 0.76 after correction for optimism. This study identified a substantial group of vulnerable patients in ambulatory surgery. The proposed clinical prediction model could allow healthcare professionals the opportunity to identify vulnerable patients in ambulatory surgery, although additional modification and validation are needed.

INTRODUCTION

Ambulatory surgery is increasing in the Western world in parallel with improved surgical safety due to advancements in anesthesia and surgical techniques. Perioperative morbidity and mortality in adult ambulatory surgery is less than 0.1%.[1] Quality of life, along with endpoints like pain and transient loss of function, has become a more important clinical endpoint in ambulatory surgery, which is dominated by psychological outcome parameters such as anxiety, aggression, fatigue, and depression.[2] Over the last decades, prediction research has been performed on somatic outcomes in ambulatory surgery patients,[1,3-5] but prediction models tailored to psychological outcomes are lacking. Nevertheless, poor psychological outcomes in patients can have negative socioeconomic consequences due to prolonged convalescence that delays a return to normal activities and work.[6-10]

Accordingly, it is of clinical interest to predict which patients are at risk of psychological vulnerability after ambulatory surgery. Patients are considered vulnerable if they deviate substantially from the norm in terms of their psychological outcome parameters. If psychological vulnerability can be predicted before surgery, appropriate action could be taken as needed to improve outcomes after ambulatory surgery.

The objective of this study was to create and test a model that identifies psychologically vulnerable ambulatory surgery patients. Towards this end, we constructed and validated a clinical prediction model that included sociodemographic, medical, and psychological determinants.

METHODS

The study protocol was approved by the Medical Ethics Committee of Erasmus University Medical Center and by the Netherlands Central Committee on Research Involving Human Subjects. It was registered with EudraCT (#2010-020332-19). Written informed consent was obtained from all subjects.

Study population

This study comprises data from a larger randomized clinical trial published previously,[2] and parts of this Methods section were adapted to address the different objectives of the current study.

Briefly, 400 patients were recruited from our ambulatory surgery department during

October 2010 to September 2011. Inclusion criteria were patients who were at least 18 yr of age and referred for ambulatory surgery. Exclusion criteria were patients who clearly had an insufficient command of the Dutch language or an intellectual disability, patients undergoing procedures generally considered less invasive (i.e., ophthalmology surgery, extracorporeal shock wave lithotripsy, endoscopy, Botox treatment, abortion, or chronic pain), those who previously used psychopharmaceuticals, and those with contraindications to the use of lorazepam. Patients were randomized to either the lorazepam group or the placebo (NaCl 0.9%) group in the original randomized-controlled trial (RCT). Healthcare professionals, patients, and researchers were all blinded to the medication given.

Procedure and intervention

All patients scheduled for ambulatory surgery received written information about the trial at least one week before surgery. A member of the research group enrolled patients after their admission to the ambulatory surgery centre and sought written informed consent. Patients who consented to participate completed a set of online questionnaires while waiting for surgery (T0). The study medication was then administered in the preoperative holding period. On the sixth day after surgery, one of the researchers telephoned the patients to remind them to complete the last set of online questionnaires the next day (T1).

Outcome variables

Anxiety was measured using the Dutch version of the State-Trait Anxiety Inventory (STAI).[11] The STAI consists of two 20-item scales. One scale measures how people generally assess their feelings, i.e., trait anxiety (STAI-T), and the other scale measures how people assess their feelings at the present moment, i.e., state anxiety (STAI-S). Sum scores for both scales are calculated by summing the scores for the items. The theoretical range is from 20-80, with a higher score indicating a higher level of anxiety. The STAI has good validity, and the STAI-S and STAI-T scales have overall similar reliability scores, with Cronbach's $\alpha > 0.80$.[11]

Aggression regulation was assessed using the Dutch translated version of the State-Trait Anger Scale (STAS),[12] which consists of two ten-item scales. One scale measures state aggression, i.e., how people assess their anger intensity at the moment (STAS-S), and the other scale measures trait aggression, i.e., how people generally assess their anger intensity (STAS-T). Sum scores for both scales are calculated by summing the scores for the items. The theoretical range is from 10-40, with a higher score indicating a

higher level of aggression. Both subscales have adequate validity, and both the STAS-S and the STAS-T have good reliability scores, with Cronbach's α values of 0.93 and 0.88, respectively.[12]

Fatigue was measured using the Dutch version of the Multidimensional Fatigue Inventory (MFI),[13] a 20-item questionnaire that comprises five four-item scales: general fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activity. Sum scores are calculated by summing the scores for the items. The theoretical range is from 20-100, with a higher score indicating a higher degree of fatigue. In the majority of cases, the MFI has good validity and reliability, with Cronbach's α exceeding 0.80.[13]

Depressive moods were measured using a Dutch translated version of the Hospital Anxiety and Depression Scale (HADS),[14] which consists of two seven-item scales. One scale measures anxiety (HADS-A), and the other scale measures depression (HADS-D). Sum scores for both scales are calculated by summing the scores on the items. The theoretical range is from 0-21, with a higher score indicating moods that are more depressive. The HADS has adequate validity and internal consistency in the Dutch population (Cronbach's α = 0.88).[15]

All outcomes were assessed at T1 (postoperative day 7).

Determinants

The sociodemographic candidate determinants were sex, age, educational level, marital status, employment, religion, having children, and type of nationality. The medical candidate determinants were body mass index (BMI) and preoperative heart rate. Psychological candidate determinants included all baseline assessments of the psychological outcome variables, self-esteem, and self-efficacy.

Self-esteem was measured using the Dutch version of the Rosenberg Self-Esteem Scale (RSES).[16] Sum scores are calculated by summing the scores on the items. The theoretical range is from 10-40, with a higher score indicating a higher degree of self-esteem. The RSES has good validity and reliability (Cronbach's α = 0.87).[16]

Self-efficacy was measured using the Dutch version of the General Self-Efficacy Scale (GSES).[17] Sum scores are calculated by summing the scores for the items. The theoretical range is from 10-40, with a higher score indicating a higher degree of self-esteem. The GSES has adequate validity and good reliability (Cronbach's α = 0.85) in the Dutch population.[18]

All determinants were assessed at T0 (preoperatively).

Definition of vulnerability

According to recent research in our field, use of constructed composite scales according to normative data is a practical way to screen for postoperative psychological outcomes.[19] We used the 84th percentile cut-off as, to date, this is normally applied in clinical prediction studies to identify aberrant patients.[20-22] Thus, likewise, patients in the present study were considered vulnerable after surgery if they scored a standard deviation (SD) of ≥1 above the mean in the normal population on the outcome variables. The mean (SD) norm scores were as follows: STAI-S, 34.8 (8.4); STAI-T, 36.9 (8.4); MFI, 41.1 (16.1); STAS-S, 11.2 (3.1); STAS-T, 16.7 (4.0); HADS-A, 5.1 (3.6); and HADS-D, 3.4 (3.3).[11,12,23,24] The literature does not report norm scores for STAI and STAS, so these were obtained from the Dutch manual using the students' category as the most appropriate reference group. Vulnerability was subsequently calculated on how many of the seven outcome parameters a patient scored in the vulnerability region. Consequently, vulnerability scores could range from 0 (not at all vulnerable) to 7 (vulnerable for all seven outcome variables). Patients were categorized as non-vulnerable (V0, vulnerability score 0), single vulnerable (V1, vulnerability score 1), and multiple vulnerable (V2, vulnerability score ≥ 2).

Statistical analysis

Of the 400 patients enrolled in the original RCT, data from 398 patients were eligible for analysis.[2] Of these, 383 patients completed the measurements on the seventh day after surgery. We calculated percentages and means as measures of a central tendency for determinants and outcome variables in these 383 patients. For continuous data, the standard deviation was presented as a measure of dispersion. Analyses were adjusted for the intervention as randomized together with the type of surgical specialty and the type of anesthesia.

Modelling strategy and validation

Ordered polytomous logistic regression analysis was used to develop the prediction model. All determinants were included in the model followed by a backward elimination procedure (*P*-to-remove > 0.20). Akaike's Information Criterion was evaluated during the modelling procedure. The final model was subjected to bootstrapping (1,000 times) for internal validation.[25] The discriminative ability of the resulting prediction model was measured using the ordinal *c*-index (ORC).[26] The ORC can be interpreted as the probability to rank cases correctly from two randomly selected categories. If a

model orders patients randomly, the ORC is equal to 0.5; with perfect ordering, the ORC is equal to 1. Lorenz curves were constructed to visualize discrimination between the vulnerability categories.[27] The Lorenz curve can well be used in clinical research to indicate discrimination between diseased and non-diseased states.[28]

Overall model performance was measured using Nagelkerke's R^2.[29] All performance measures were corrected for optimism by bootstrapping (i.e., internal validation).[25] We used SPSS version 20.0 (IBM Corp., Armonk, NY, USA) for statistical analyses. Performance measures were calculated in R version 3.0.1.[30] Results were considered statistically significant if the two-sided P was < 0.05.

RESULTS

Patients

We found that 137 (36%) of the 383 ambulatory surgery patients were psychologically vulnerable, with 76 patients being single-domain vulnerable and 61 patients being multiple-domain vulnerable after surgery (Table 1). In the non-vulnerable group, 61% (n = 150) were male, whereas in both the single and multiple vulnerable groups, 50% were male. In all vulnerability categories, the majority of the patients had a middle-level education. Most patients were employed, and more than half of the patients lived with a partner. Patients of Dutch nationality dominated the study population (Table 2).

TABLE 1 | Vulnerability categories

Vulnerable points	*n*	%
None	246	64.2
One	76	19.8
Two	27	7.0
Three	10	2.6
Four	13	3.4
Five	5	1.3
Six	4	1.0
Seven	2	0.5

White, Non-vulnerable patients (V_0); light gray, single vulnerable patients (V_1); dark gray, multiple vulnerable patients (V_3).

TABLE 2 | Descriptions of baseline determinants distinghuished by vulnerability category

Baseline determinants	Vulnerability categories					
	None (n=246)		Single (n=76)		Multiple (n=61)	
Categorical variables	*n*	*%*	*n*	*%*	*n*	*%*
Sex (male)	150	61.0	38	50.0	31	50.8
Education						
Middle	162	65.9	54	71.1	43	70.5
High	47	19.1	11	14.5	5	8.2
Employment (having)	193	78.5	57	75.0	39	63.9
Marital Status (together)	158	64.2	43	56.6	34	55.7
Children (yes)	124	50.4	35	46.1	40	65.6
Religion (yes)	74	30.1	24	31.6	26	42.6
Nationality (Dutch)	233	94.7	69	90.8	57	93.4
Continuous variables	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
Age	40.0	14.3	38.4	12.8	39.8	12.3
BMI	25.1	4.2	25.4	4.1	25.8	4.0
Heart rate	70	13	72	13	71	13
STAI-S (20–80)*	35.7	8.8	40.7	9.6	43.3	8.9
STAI-T (20–80)*	30.9	6.2	35.4	7.7	41.8	9.2
STAS-S (10–40)*	10.1	0.7	10.3	1.4	10.5	2.2
STAS-T (10–40)*	12.7	2.9	14.0	3.7	15.6	4.8
MFI (20–100)*	36.8	10.6	48.2	12.4	52.0	13.5
HADS-A (0–21)*	3.8	2.5	5.5	3.3	7.1	3.6
HADS-D (0–21)*	2.4	1.9	3.3	2.3	5.3	3.1
RSES (10–40)*	34.4	3.9	32.8	4.5	30.9	5.1
GSES (10–40)*	32.0	4.1	30.9	4.2	30.9	4.2

Observed values, assessed at baseline. BMI, body mass index; STAI-S, State-Trait Anxiety Inventory, State part; STAI-T, State-Trait Anxiety Inventory, Trait part; STAS-S, State-Trait Anger Scale, State part; STAS-T, State-Trait Anger Scale, Trait part MFI, Multidimensional Fatigue Inventory; HADS-A, Hospital Anxiety and Depression Scale, Anxiety part; HADS-D, Hospital Anxiety and Depression Scale, Depression part; RSES, Rosenberg Self-Esteem Scale; GSES, General Self-Efficacy Scale. *(xx-xx) reflects the score range for that particular measurement. SD, standard deviation.

TABLE 3 | Univariate and multivariable odds ratios

	Univariate		Multivariable	
	OR* (95% CI)		OR*(95% CI_b)	
Categorical variables				
Sex	1.50	(0.99 to 2.27)		
Education				
Middle	0.81	(0.46 to 1.42)	1.73	(0.88 to 4.24)
High	0.44	(0.20 to 0.94)	1.92	(0.74 to 6.18)
Employment	0.56	(0.35 to 0.89)		
Marital Status	0.72	(0.47 to 1.10)		
Children	1.35	(0.89 to 2.04)	1.97	(1.13 to 3.63)
Religion	1.45	(0.94 to 2.24)		
Nationality	0.78	(0.35 to 1.77)	2.40	(0.76 to 9.89)
Continuous variables				
Age	1.00	(0.98 to 1.01)		
BMI	1.03	(0.98 to 1.08)		
Heart rate	1.01	(1.00 to 1.03)		
STAI-S	1.07	(1.05 to 1.10)		
STAI-T	1.15	(1.11 to 1.18)	1.08	(1.03 to 1.15)
STAS-S	1.21	(1.01 to 1.45)	1.19	(0.89 to 1.62)
STAS-T	1.17	(1.10 to 1.24)	1.06	(0.97 to 1.14)
MFI	1.09	(1.07 to 1.11)	1.06	(1.03 to 1.09)
HADS-A	1.31	(1.21 to 1.40)		
HADS-D	1.43	(1.30 to 1.57)	1.17	(1.01 to 1.36)
RSES	0.87	(0.83 to 0.91)		
GSES	0.95	(0.90 to 1.00)		

Estimated values are adjusted for type of intervention as randomized, type of surgical specialty, and type of anesthesia. Multivariable model's OR (95% CI_b) for type of intervention as randomized (0=placebo, 1=lorazepam) is 1.47 (0.88 to 2.52). Used method: ordered polytomous logistic regression analysis; link function: logit. BMI, body mass index; STAI-S, State-Trait Anxiety Inventory, State part; STAI-T, State-Trait Anxiety Inventory, Trait part; STAS-S, State-Trait Anger Scale, State part; STAS-T, State-Trait Anger Scale, Trait part; MFI, Multidimensional Fatigue Inventory; HADS-A, Hospital Anxiety and Depression Scale, Anxiety part; HADS-D, Hospital Anxiety and Depression Scale, Depression part; RSES, Rosenberg Self-Esteem Scale; GSES, General Self-Efficacy Scale. *OR, odds ratio; The ORs of psychological instruments are per unit increase in the score. CI, confidence interval. CI_b, 1000 times bootstrapped confidence interval.

The mean range of values for age (38.4-40.0) yr, BMI (25.1-25.8) kg*m^{-2}, and preoperative heart rate (70-72) beats*min^{-1} were nearly equally distributed in the three vulnerability categories. As expected, preoperative anxiety, aggression, fatigue, and depression scores were lowest in the non-vulnerable group and highest in the multiple vulnerable group. Similarly, the self-esteem and self-efficacy scores were worse in the multiple vulnerable group (Table 2).

Univariate and multivariable analyses

Table 3 presents the univariate and multivariable odds ratios (ORs) of the candidate determinants in the clinical prediction model. We focused on the ORs of the determinants in the multivariable prediction model. The level of education was an important predictor for vulnerability (OR for a middle-level education, 1.73; 95% confidence interval [CI], 0.88 to 4.24; OR for a high-level education, 1.92; 95% CI, 0.74 to 6.18). Other Important sociodemographic predictors were having children (OR, 1.97; 95% CI, 1.13 to 3.63) and Dutch nationality (OR, 2.40; 95% CI, 0.76 to 9.89).

None of the medical determinants were relevant in the multivariable model. In contrast, various psychological determinants were important predictors of psychological vulnerability. Higher anxiety, aggression, fatigue, and depression scores seemed to be associated with a higher risk of psychological vulnerability after surgery (Table 3).

Model performance

The overall model performance was good (Nagelkerke's R^2, 41%; 30% after correction for optimism). The discriminative ability of the final prediction model was also promising, with an ORC of 0.80 (0.76 after correction or optimism). The Figure illustrates the practical use of the prediction model. If we aim to correctly identify 50% of those who are vulnerable, we correctly label about 90% of the non-vulnerable patients as being non-vulnerable (Figure 1).

DISCUSSION

Study results indicated that, based on the scores for the four psychological outcome parameters (i.e., anxiety, aggression, fatigue, and depression), more than one-third of our study population showed poor psychological outcomes one week after ambulatory surgery. We constructed and validated a clinical prediction model to identify these vulnerable patients. The final prediction model combined sociodemographic (i.e., level of education, having children, and nationality) and psychological determinants (i.e.,

trait anxiety, state/trait aggression, fatigue, and depression) and had promising overall performance and discriminative ability.

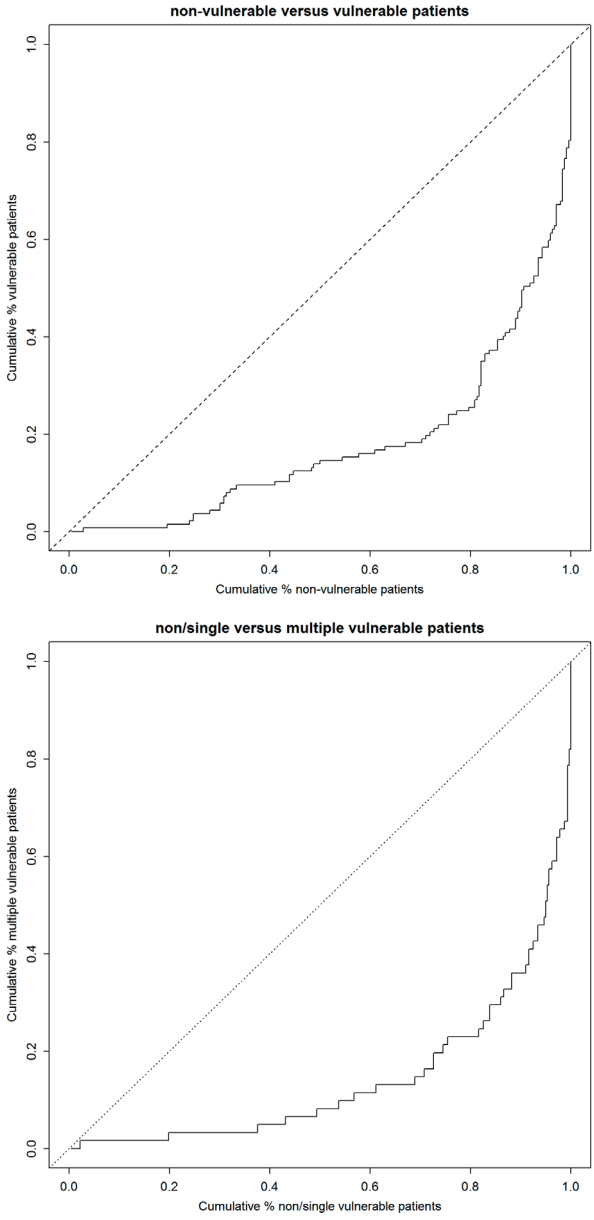

FIGURE 1| Lorenz curves for 383 patients enrolled in a randomized-controlled trial

The graphs show the relation between the cumulative proportion of patients who are classified as non-vulnerable while they are vulnerable (y-axis, Figure A) vs classified as non-vulnerable among the non-vulnerable patients. Figure B) classification as non-vulnerable or as scoring only one vulnerable outcome vs multiple vulnerability.

Model considerations

We developed a multivariable model with nine independent variables, four of which had statistically significant ORs. Interestingly, with respect to the psychological determinants, STAI-T (trait anxiety) was the only one of the three anxiety questionnaires (i.e., STAI-S, STAI-T, and HADS-A) included in the final prediction model. This suggests that these tests assess not only common elements but also unique elements. Furthermore, it is known that STAI-T assesses negative affectivity next to anxiety.[31]

With respect to the sociodemographic determinants, we found that level of education was somewhat paradoxically related to vulnerability. Specifically, in univariate analysis, patients with a low level of education were more likely to be vulnerable. In contrast, more highly educated patients were more likely to be vulnerable in the multivariable analysis. To exclude the possibility that this was a statistical artefact due to high correlation between determinants (i.e., multicollinearity), the variance inflation factor (VIF) should be evaluated. The VIF quantifies the degree to which multicollinearity among the determinants degrades the precision of estimate coefficients.[32] Multicollinearity negatively affects the results and the reliability of the regression estimates.[32] Generally, a VIF value exceeding 4.0 is considered to threaten valid statistical inferences. We therefore checked the multicollinearity, but we found that the VIF did not exceed 2.1. Further analyses suggested that the change in the impact of education on psychological vulnerability emerged when, in addition to demographic variables, trait anxiety was included in the prediction model. This effect was not found in analyses with the other psychological variables. One possible explanation is that patients with low levels of education are masking (i.e., giving socially desirable answers about) their anxiety, which is considered as "social desirability" in the psychological literature.[33,34] Alternatively, they may recognize their feelings of anxiety to a lesser degree –i.e., using denial as a defence mechanism. This latter psychological adjustment is well known in, for example, cancer research.[35] Furthermore, it could be that a spurious correlation emerged and that more educated patients really did have more anxiety. We emphasize that these results could be due to statistically random fluctuations.

Likewise, type of nationality turned out to be paradoxically in the analysis. Interpretations should be cautious as the Dutch nationality highly dominated the study population –i.e., our study population consisted of only 24 non-Dutch patients, making our estimate of this effect quite unstable.

Future considerations

As one-third of our study patients showed poor psychological outcome, more attention should be paid to psychological outcome parameters as clinical endpoints. Furthermore, to improve the quality of care in ambulatory surgery and to avoid negative socioeconomic effects,[6-10] patients who are vulnerable according to these psychological outcome parameters should be prepared adequately before surgery. This is a task that could be managed by anesthesiology departments, since preoperative risk assessment is a specific task of anesthesiologists, and optimizing treatment can enhance postoperative recovery.[36,37]

One method of preparing vulnerable patients could be treatment with premedication. Nevertheless, from previous studies, we know that solitary treatment with premedication, e.g., administration of benzodiazepines prior to surgery, is insufficient to improve the quality of recovery,[2,38,39] although more research is needed to clarify the effectiveness of premedication with benzodiazepines on psychological outcomes in ambulatory surgery.[40] Consequently, non-drug treatments, such as psychological preparation, seem more appropriate. In ambulatory surgery, preoperative psychological preparation could include several approaches,[41] including written, video, and/or visit information.[41] In particular, video information would provide the patient with a better understanding of the medical intervention.[42,43]

These methods could be implemented within, for example, a multimodal prehabilitation program that has physical, nutritional, and psychological aspects. The prehabilitation programs could enhance postoperative recovery using preoperative interventions tailored to the population of interest.[44-47] Because ambulatory surgical procedures are planned well in advance, a prehabilitation program could be considered to treat these vulnerable patients. Currently, however, there is a lack of prehabilitation programs for ambulatory surgery.

Such methods could also be adjusted and tailored to the postoperative period and perhaps incorporated into the rehabilitation program. Rehabilitation programs are multimodal programs that predominantly intervene in the postoperative period to enhance postoperative outcome.[48] Such programs have been shown to be effective in different surgical populations.[48-50] It has also been suggested that rehabilitation programs should be reserved for patients who require postoperative care after the prehabilitation program.[47]

If these multidisciplinary prehabilitation and rehabilitation programs are implemented,

anesthesiologists should play a prominent role in their management.[51] Development of a risk stratification model is highly recommended so that the program could be tailored to different sets of patients.[44] Using our prediction model, risk stratification for the ambulatory population may become feasible, and stratification could guide decision-making. Presumably, patients identified as single-domain vulnerable would need a different treatment plan than those identified as multiple-domain vulnerable. The Appendix illustrates the clinical application of the constructed clinical prediction model for two clinical cases.

There should be further investigation as regards the clinical importance of these findings in terms of the identified vulnerabilities. Additional research is also needed to investigate which treatment is required for vulnerable patients; furthermore, a cost-effectiveness analysis should be performed.

Using this prediction model requires some effort, and therefore, future studies could be tailored to minimize this effort. Future studies could also investigate whether determinants associated with "bad" habits (e.g., smoking, alcohol and drug usage, excessive eating, sedentary lifestyle, etc.) are manifestations of psychological vulnerability. It would also be interesting to investigate the influence of interpersonal variables, since previous research shows that these variables are also important care characteristics.[52] In addition, preoperative mental health screening could be considered, especially with regard to more severe (surgical) populations. One essential step is to acquire external validation for our model in independent sets of patients, which may indicate the need for modifications.[32]

Study limitations and strengths

Our study has some limitations. First, 15 patients were not analyzed due to lack of outcome data. These patients could be vulnerable and therefore unable to complete the measurements one week after surgery. Second, in the original RCT, patients were excluded due to use of psychopharmaceuticals or because they were undergoing certain surgical procedures, e.g., abortion, which were stressful for these patients.[2] It is plausible that these patients may be more susceptible to the psychological events that could be elicited by a surgical procedure. Therefore, we expect that the actual percentage of vulnerable patients in ambulatory surgery may be higher than 36%. This does not imply that the final prediction model should be changed accordingly. Finally, this was a single-centre study, and the generalizability of the model needs to be studied.

The main strength of our study is that it uses high-quality data from a randomized trial. In addition, we internally validated our prediction model. Detection of vulnerability was based on tests that are all psychometrically validated in psychomedical fields. Therefore, we do not assume that we have necessarily underdiagnosed vulnerability in this surgical population.

CONCLUSION

This study identified a substantial group of vulnerable patients in ambulatory surgery. The proposed clinical prediction model is a first step in predicting poor psychological outcome after ambulatory surgery, although additional modification and validation are needed. The model could allow healthcare professionals, especially anesthesiologists, the opportunity to identify vulnerable patients in ambulatory surgery who would benefit from specific interventions.

APPENDIX 1

In this manuscript, we constructed the following clinical prediction model:

$$Y = \beta_0 + \beta_{Educ1} \times Educ1 + \beta_{Educ2} \times Educ2 + \beta_{Children} \times Children + \beta_{Nationlaity} \times Nationality + \beta_{STAI\text{-}T} \times STAI\text{-}T + \beta_{STAS\text{-}S} \times STAS\text{-}S + \beta_{STAS\text{-}T} \times STAS\text{-}T + \beta_{MFI} \times MFI + \beta_{HADS\text{-}D} \times HADS\text{-}D$$

$\beta_0 = 10.223$ (threshold 0) or 11.823 (threshold 1)

$\beta_{educ1} = 0.546$; $\beta_{educ2} = 0.653$; $\beta_{Children} = 0.676$; $\beta_{Nationality} = 0.876$; $\beta_{STAI\text{-}T} = 0.078$; $\beta_{STAS\text{-}S} = 0.177$; $\beta_{STAS\text{-}T} = 0.059$; $\beta_{MFI} = 0.057$; $\beta_{HADS\text{-}D} = 0.153$

Application clinical prediction model – Case 1

Miss X, born at 01-02-1970 in Rotterdam where she has been living. She has been married and gave birth to two children. She completed primary school only. Preoperatively, she showed the following results on the questionnaires:

STAI-S	25
STAI-T	23
STAS-S	12
STAS-T	10
MFI	30
HADS-A	3
HADS-D	5
GSES	35
RSES	35

Her estimated risk of being non-vulnerable, single-vulnerable and multiple vulnerable equals 84%, 12% and 4% respectively.

Application clinical prediction model – Case 2

Mr Y, born at 03-04-1972 in Rotterdam where he has been living. This single man has no children. He graduated from university and works as a lawyer. Preoperatively, he showed the following results on the questionnaires:

STAI-S	40
STAI-T	45
STAS-S	17
STAS-T	12
MFI	40
HADS-A	12
HADS-D	10
GSES	15
RSES	20

His estimated risk of being non-vulnerable, single-vulnerable and multiple vulnerable equals 9%, 23% and 68% respectively.

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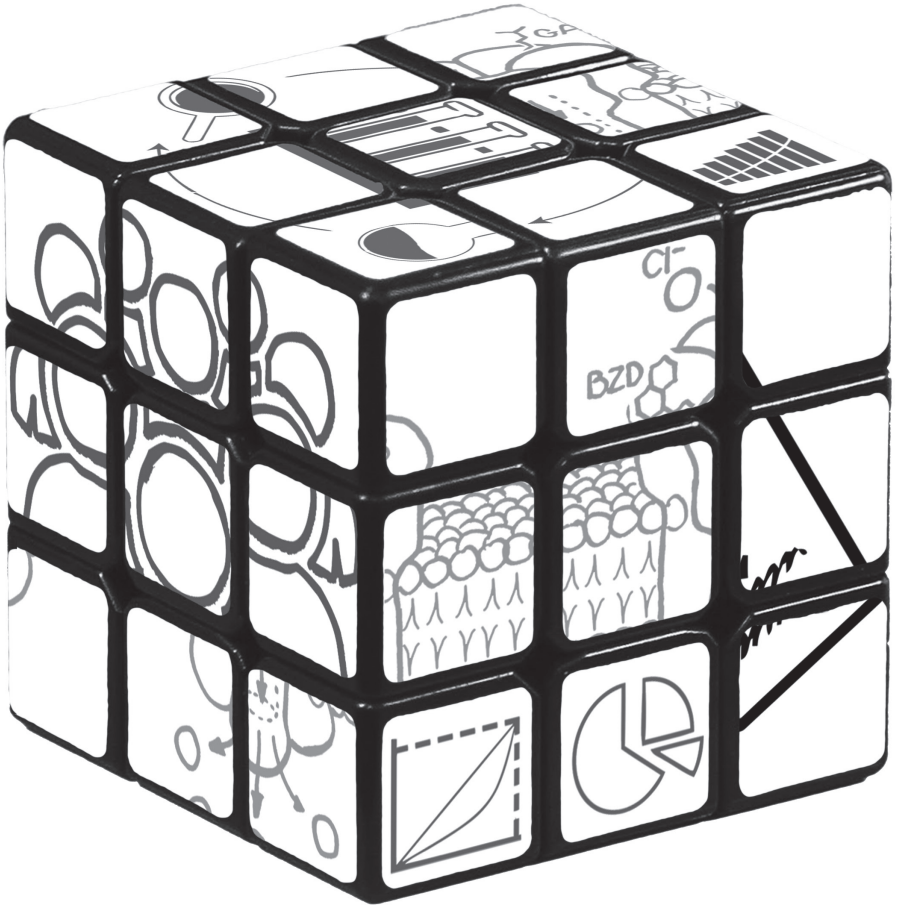
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POTENTIAL PATHWAYS LEADING TO POSTOPERATIVE FATIGUE: STRUCTURAL EQUATION MODELING IN DAY-CASE SURGERY PATIENTS

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CHAPTER 7

Submitted

ABSTRACT

Postoperative fatigue is common following surgery, however its etiology is still unknown. The most common theory to date is of psychological nature assuming that anxiety and depression are closely related to fatigue. Although these factors are indeed strongly interrelated, direction of causality is currently not determined which is necessary for proper treatment. We tried to unravel the direction of these pathways using an appropriate statistical methodology in order to find a target for treatment or prevention. Structural equation modeling was used to unravel the pathways among fatigue, anxiety, and depression in 398 mixed adult patients undergoing day-case surgery. Assessments took place preoperatively and postoperatively. Fatigue was measured using the Multidimensional Fatigue Inventory, whereas anxiety and depression were measured using the Hospital Anxiety and Depression Scale. Standardized regression coefficients (B) were used as measures of relative importance. The most optimal path model showed that preoperative fatigue substantially predicted postoperative fatigue (B = 0.54, *P* = 0.00), and that preoperative anxiety and depression were unimportant in predicting postoperative fatigue. Furthermore, at each single measurement moment fatigue significantly predicted anxiety and depression rather than vice versa. The model fit was adequate: χ^2 16.10, df 9, *P* = 0.06, CFI 0.991, TLI 0.979, SRMR 0.029, RMSEA 0.045.
In the day-case surgery population postoperative fatigue is likely induced via preoperative fatigue, and not a consequence of anxiety and depression. If an intervention for postoperative fatigue is considered, preoperative treatment tailored to reduce preoperative fatigue could be strategy of choice.

INTRODUCTION

Postoperative fatigue is a widespread problem in nowadays society. Postoperative fatigue considerably negatively affects the physical and psychosocial condition of patients.[1] Furthermore, it also leads to unwanted economic effects because postoperative fatigue could prolong the convalescence period delaying return to normal daily activities.[1,2] Postoperative fatigue seems to emerge substantially among patients undergoing a broad range of surgical procedures including major abdominal, gynaecological, cardiac surgery, and even after minor surgery.[3] The incidence of postoperative fatigue varies among these different types of surgery, and at specific time points in the convalescence period which may accumulate up to 92%.[3] To cope with this, most patients complain with their general practitioner or with their surgeon. Hence, numerous studies have aimed to find the underlying cause of postoperative fatigue but the etiology remains inconclusive. These studies resulted in two different theories, namely a physiological and a psychological theory. The physiological theory assumes that postoperative fatigue originates from the surgical response to trauma.[4] The psychological theory – most commonly accepted to date – assumes that anxiety and depression are misinterpreted as fatigue in the postoperative period.[5] In day-case surgery the latter theory is most likely because the surgical response to trauma is minimized by the nature of the procedures, use of minimal invasive surgical techniques, and advanced anesthetic techniques using short acting drugs. Furthermore, fatigue, anxiety, and depression are strongly interrelated in the postoperative period.[5-7] However, the direction of causality between these phenomena is not yet determined.[7,8] If we would be able to unravel the directions of the pathways between fatigue on the one hand and anxiety and depression on the other hand, patient treatment could be more directed to the primary cause. For this purpose, appropriate statistical methodology, such as structural equation modeling (SEM), was previously proposed.[8] This method has been shown to be a suitable statistical method to unravel potential clinical pathways.[9,10]

The objective of this study was to unravel the directions of the pathways between fatigue on the one hand and anxiety and depression on the other hand in a day-case population using SEM. Secondly, the objective was to find a target for treatment in order to prevent postoperative fatigue according to the identified pathway.

METHODS

This study used data from a larger randomized placebo-controlled clinical trial evaluating the postoperative effectiveness of preoperative administered lorazepam.[11] The study protocol was approved by the Medical Ethics Committee of Erasmus MC and

by the Netherlands Central Committee on Research Involving Human Subjects (CCMO). It was registered with EudraCT (#2010-020332-19). The original trial was also registered in the ClinicalTrials.gov protocol registration system (#NCT01441843). Written informed consent was obtained from all subjects. In order to address the different objectives of this paper, we have adapted parts of the methods section.

Study population

Consecutive adult patients undergoing day-case surgery at the Erasmus University Medical Center, Rotterdam, The Netherlands, were invited to participate in this study. Patients were excluded if they clearly had an insufficient command of the Dutch language or intellectual disability, or were undergoing ophthalmology surgery, extracorporeal shock wave lithotripsy, endoscopy, botulinum toxin A treatment, abortion or chronic pain treatment. Furthermore, preceding use of psychopharmaca or any contraindication to lorazepam use served as exclusion criteria.

Study design

Measurements were performed preoperatively on the day of surgery (T0) and postoperatively at the seventh day after surgery (T1).

Study measures

Fatigue was measured with the Dutch version of the Multidimensional Fatigue Inventory (MFI), a 20-item questionnaire covering five scales (4 items): General fatigue, Physical fatigue, Mental fatigue, Reduced motivation and Reduced activity.[12] Sum scores were calculated, which theoretically could range from 20 to 100. A higher score indicates a higher degree of fatigue. MFI has a promising validity and a good reliability in the majority of cases (Cronbach's $\alpha > 0.80$).[12]

Anxiety and depression were measured by a Dutch translated version of the Hospital Anxiety and Depression Scale (HADS), which consists of two 7-item scales, i.e. one for anxiety (HADS-A) and one for depression (HADS-D).[13] For each scale the sum score was calculated which theoretically could range from 0 to 21. A higher score indicates a higher degree of anxiety and/or depressive moods. In the Dutch population, HADS is known to have a good validity and high internal consistency (Cronbach's $\alpha = 0.88$).[14]

Analysis

We used SEM to unravel the directions of the pathways among fatigue on the one

hand and anxiety and depression on the other hand.[15] It is desirable to have a minimal subject:parameter ratio of 10:1.[15] This study clearly fulfils this criterion. We used maximum likelihood estimation during the model generation procedure.

Unravelling the pathways among fatigue, anxiety and depression

In the day-case surgery population it is difficult to hypothesize a path model because research on fatigue, anxiety, and depression is scarce. Therefore we used a more explorative way to unravel the pathways: we evaluated all possible models.[15] According to the three study measures of interest, eight pathways (2^3) are possible at each single measurement moment (lag 0). Consequently, we evaluated 64 (2^3 times 2^3) models in total. In these model evaluations, the pathways from fatigue to anxiety and depression and vice versa across time (lag 1) were left free, meaning that they were estimated. Autoregressions of the study measures across time were always estimated. Figure 1 shows the structure of the hypothesized models.

In the next step, at lag 1, we evaluated whether it was statistically allowed to restrict the pathways from preoperative fatigue to postoperative anxiety and postoperative depression; and the pathways from preoperative anxiety and preoperative depression to postoperative fatigue in order to find the most parsimonious model.

We want to emphasize that anxiety and depression were empirically measured separately – hence this is symbolized as a square in the Figure. However, according to the study objective (i.e. to unravel the directions of the pathways between fatigue on the one hand and anxiety and depression on the other hand), anxiety and depression are jointly related to fatigue – hence this is symbolized as a rectangle in the Figure. Accordingly, if a pathway runs from preoperative anxiety to postoperative fatigue the pathway starting with preoperative depression also runs to postoperative fatigue and vice versa. Thus, if the pathway from preoperative anxiety to postoperative fatigue was restricted, the pathway starting with preoperative depression running to postoperative fatigue was also restricted.

The pathways between anxiety and depression at lag 1 were left free, because these pathways were not of interest according to the study aim. Next to identification of the most plausible model, rivalling models were evaluated.

The most plausible model was then adjusted for type of intervention as randomized to control for possible confounding and subjected to bootstrapping using 1000 samples with replacement for internal validation;[16] 95% bias-corrected bootstrap confidence

intervals were calculated for unstandardized regression coefficients. The final model was estimated with the MLR estimation method (i.e. maximum likelihood estimation with robust standard errors). Standardized regression coefficients (B) were used as estimates of relative importance (theoretical range, -1.0 to 1.0). Effect sizes can be reasonably estimated in combination with significance testing, which also takes into account sample size and intercorrelations among variables. Explained variances of study measures are presented.

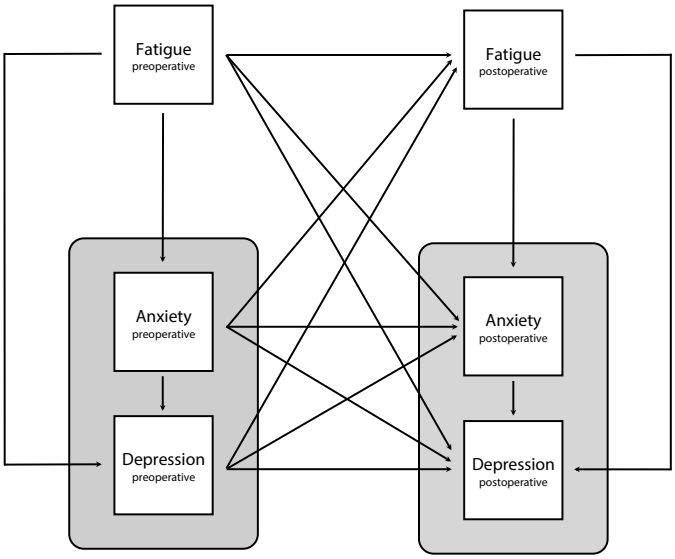

FIGURE 1 | Hypothesized path models for one measurement moment (lag 0):
A. anxiety on fatigue; depression on fatigue; depression on anxiety
B. anxiety on fatigue; depression on fatigue; anxiety on depression
C. anxiety on fatigue; fatigue on depression; depression on anxiety
D. anxiety on fatigue; fatigue on depression; anxiety on depression
E. fatigue on anxiety; depression on fatigue; depression on anxiety
F. fatigue on anxiety; depression on fatigue; anxiety on depression
G. fatigue on anxiety; fatigue on depression; depression on anxiety
H. fatigue on anxiety; fatigue on depression; anxiety on depression
Bold is shown in the figure.

Model fit

The following measures were used to test for adequacy of the model fit:
X^2 for model fit (low and non-significant values of the χ^2 are desired; *P*-value > 0.05); χ^2/df ratio (a value <2.0 was considered to be acceptable); information criteria including Akaike (AIC), Bayesian (BIC), sample-size adjusted BIC; Comparative Fit Index (CFI), and Tucker-Lewis Index (TLI). High values are desired (> 0.95);[17,18] Root Mean Square Error of Approximation (RMSEA: a value <0.05 indicates a close fit);[19] and Standardized Root

Mean Squares of Residuals (SRMR: a value of <0.08 indicates a reliable fit).[20]

We used SPSS version 20.0 (IBM Corp. Armonk, NY) and Mplus version 7 (Muthén and Muthén, Los Angeles, CA) for statistical analyses. Estimates were regarded statistically significant if the two-sided *P*-value was <0.05.

RESULTS

The study population consisted of 224 males and 174 females. The mean age equalled 39.4 years with a standard deviation of 13.6. More sociodemographic and clinical characteristics of the patients can be found elsewhere.[11]

Analysis

According to the measures for adequacy of the model fit, the results of the 64 models were inconclusive. Following parsimonious modeling, we decided to keep the pathways equal at lag 0 (i.e. at T0 and T1). This step maintained an adequate fitting model. The remaining eight models were further evaluated showing that the pathway from fatigue to anxiety and depression was most plausible according to the measures for adequacy of the model fit. At lag 1, it was statistically allowed to fix the pathways from preoperative fatigue to postoperative anxiety, and preoperative fatigue to postoperative depression at 0.00. It was also statistically allowed to fix the pathways from preoperative anxiety to postoperative fatigue, and preoperative depression to postoperative fatigue at 0.00. As the pathway between anxiety and depression was ambiguous at lag 0, all rivalling models were evaluated. None of the models has been found better fitting the data than the alternatives. Therefore, we decided to intercorrelate anxiety and depression at lag 0.[15] The final model is presented in Figure 2. The model fit was promising χ^2 16.10, df 9, *P*-value 0.06, χ^2 /df 1.79, AIC 13233.66, BIC 13329.34, sBIC 13253.18, CFI 0.991, TLI 0.979, SRMR 0.029, RMSEA 0.045.

Standardized regression coefficients (B) of the study measures are shown in Table 1. Bs among fatigue, anxiety and depression showed a range from 0.28 to 0.54. Autoregressions coefficients for fatigue, anxiety and depression were 0.54, 0.42 and 0.41 respectively. 95% Bias-corrected bootstrap intervals of the unstandardized regression coefficients can also be found in Table 1.

TABLE 1 | Regression coefficients and explained variances according to the model

Study measure	B‡	β¶	95% CI_b#	R^2§
Preoperative				
Anxiety ON				0.17
Fatigue	0.42	0.10	0.08 to 0.12	
Depression ON				0.23
Fatigue	0.48	0.09	0.07 to 0.11	
Anxiety WITH				
Depression	0.35	2.10	1.45 to 2.87	
Postoperative				
Fatigue ON				0.30
Fatigue†	0.54	0.71	0.58 to 0.82	
Anxiety		Fixed at 0.00		
Depression		Fixed at 0.00		
Anxiety ON				0.45
Fatigue†		Fixed at 0.00		
Fatigue‡	0.28	0.05	0.03 to 0.07	
Anxiety	0.42	0.39	0.28 to 0.50	
Depression	0.19	0.23	0.11 to 0.35	
Depression ON				0.48
Fatigue†		Fixed at 0.00		
Fatigue‡	0.45	0.08	0.06 to 0.09	
Anxiety	0.02	0.02	-0.06 to 0.11	
Depression	0.41	0.49	0.37 to 0.62	
Anxiety WITH				
Depression	0.42	1.89	1.32 to 2.65	

Analysis adjusted for type of intervention as randomized. †Preoperative fatigue; ‡Postoperative fatigue; ‡Standardized regression coefficient; ¶unstandardized regression coefficient; #1000 times bootstrapped 95% confidence interval; § Explained variances.

DISCUSSION

The principal finding of this study was that postoperative fatigue is likely induced by the presence of preoperative fatigue. The role of preoperative anxiety and depression on postoperative fatigue may be questioned. This finding is in line with recent research in other sets of patients showing that fatigue is a primary phenomenon rather than a consequence of anxiety and depression.[21,22]

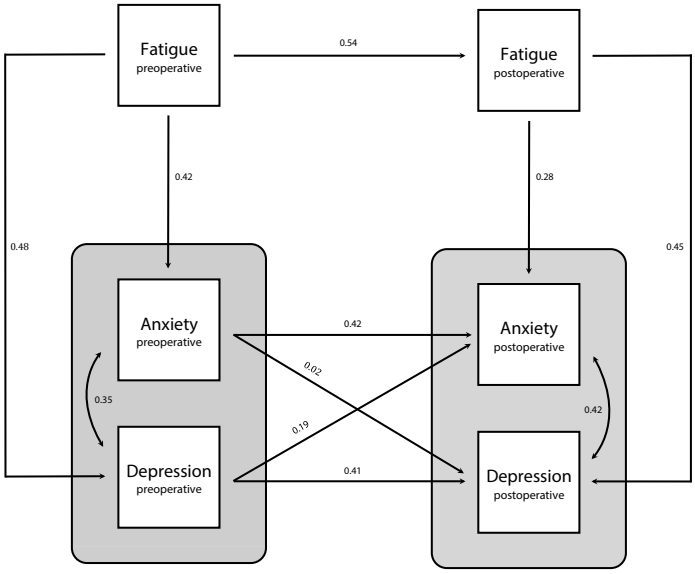

FIGURE 2 | Most parsimonious path model including standardized regression coefficients
The pathways that have been fixed at 0.00 are omitted in the figure.

Explained variances (R^2) are estimated for each study measure (Table 1). Postoperative fatigue was substantially predictable ($R^2 = 0.30$). Overall, explained variances of the final model were substantial, range 0.17 to 0.48 (Table 1).

The second observation was that our data structure showed that the role of anxiety and depression with regards to fatigue is also questioned when these variables are measured simultaneously at one measurement moment (i.e. lag 0). Although conclusions with regards to directionality should be drawn with caution by the absence of a temporal relation, recent research performing path modeling on simultaneous measurements also showed results supporting the hypothesis that fatigue is a cause and not a consequence of anxiety and depression.[22] Furthermore, in support of our model, others have showed that, although in a different patient sample, improving fatigue results in less anxiety and depression.[23]

At first sight our findings seem to contradict with the suggested psychological theory of postoperative fatigue by Salmon and Hall as mentioned in the introduction.[5] This theory states that postoperative fatigue is the result of misinterpretation of anxiety and depression in the postoperative surgical ward in inpatients. However, in day-case surgery, patients are admitted and discharged on the day of surgery. So, the medical

context may explain our deviant findings.
The next step could be to find and perform an appropriate intervention to treat postoperative fatigue in day-case surgical patients when needed. Many pre-, per- and postoperative interventions for postoperative fatigue have been designed, conducted, and reviewed systematically.[24] This review showed that improved analgesia could only significantly attenuate postoperative fatigue. A possible reason for the lack of significance of many interventions could be the wrong target of intervening. Structural equation modeling (SEM) has been shown to be able to indicate a target for intervention in order to treat fatigue after a medical process.[21] The corollary according to our SEM model is that we should focus on treating preoperative fatigue when we aim for prevention of postoperative fatigue. This could well be feasible in day-case surgery because all procedures are planned admissions, meaning that the prehabiliation period is sufficient to intervene. Surgical prehabilitation is the period of time from diagnosis to the surgical intervention in which the preoperative status of the patient can be optimized. Recently, it has been shown that prehabilitation programs are effective in enhancing postoperative recovery, and that this method is superior to the more conventional approach to intervene in postoperative period – i.e rehabilitation.[25] The content of prehabilitation programs may differ and should be adjusted to the specific requested health issue.[26]

When we aim to reduce preoperative fatigue, multimodal treatment seems indicated because it is known that fatigue has a multifactorial nature.[12,27] Multimodal prehabilitation programs could be a suitable framework to achieve this. Moreover, multimodal prehabilitation programs – with physical, nutritional, and psychological aspects – are more effective than unimodal programs.[25,28] These existing programs could be further optimized and tailored to reduce preoperative fatigue when other aspects are considered too. For example, a brief psychological relaxation treatment starting preoperatively was shown to be effective in reducing postoperative fatigue.[29] We also know that cognitive behavioural therapy is an established treatment regarding a broad range of fatigue syndromes.[30] This therapy could well be effective when it is tailored to preoperative fatigue specifically.

Pharmacological therapy could also be of interest. We know that pharmaca acting at (the precursor of) the neurotransmitter 5-hydroxytryptamine could be of interest as this is likely to be involved in the process of fatigue, anxiety and depression.[31-33] However, regarding the former, it was shown that this process was more pronounced in major surgery,[33] making this treatment likely less suitable for day-case surgery patients. Preoperative pharmacological treatment (i.e. premedication) is a frequently

used tool to prepare patients for the upcoming surgery and to improve postoperative outcome. In day-case surgery, however, premedication is administered on the day of the surgical procedure and is therefore not in time to address preoperative fatigue. Furthermore, previous research showed that premedication is not strong enough to affect postoperative fatigue positively.[11] On the other hand, a recent meta-analysis showed that more profound research is needed for firm conclusion about the effect of premedication on postoperative fatigue in day-case surgery.[34]

Recommendations for future research

This study is a first approach to unravel the directions of the pathways among fatigue, anxiety, and depression in day-case surgery using SEM. Although the fit of the identified model was adequate, our results should be confirmed in other sets of patients. Modifications in the identified model might be necessary. Furthermore, directionality between simultaneously measured study measures should be confirmed using a longitudinal design including pre- and postoperative measurements. Although prognostic research has been done in day-case surgery,[35] further work is increasingly needed to determine which patients are vulnerable (i.e. have aberrant levels of preoperative fatigue). Prognostic models and preoperative risk evaluations have to be performed to indicate which patients need additional treatment and potentially prehabilitation programs.[25] Cost-effectiveness analysis may be of incremental value. Furthermore, future research should be tailored to find predictors of preoperative fatigue instead of postoperative fatigue.

Strengths and limitations

In this work we relied on a specific statistical modeling generation technique. This non-hypothesis driven method is a strength of this study in that it allows unravelling clinical pathways in an efficient way. Furthermore, we evaluated rivalling models that could fit the data in order to avoid confirmation bias.[36] Nevertheless, decisions during the modeling procedure are a matter of judgement, and theoretically other models could be statistically tested. External validation in another (day-case) surgery population is recommended. Hence, the generalizability of the present results should be made with caution especially in a non-day-case surgery population.

CONCLUSION

In conclusion, in day-case surgery postoperative fatigue is likely induced via preoperative fatigue. The role of anxiety and depression on postoperative fatigue may be questioned.

If an intervention for postoperative fatigue is considered, preoperative treatment embedded in a prehabilitation program framework tailored to reduce preoperative fatigue seems to be the strategy of choice. Ultimately, this will lead to reduction of physical, psychosocial, and economic burden.

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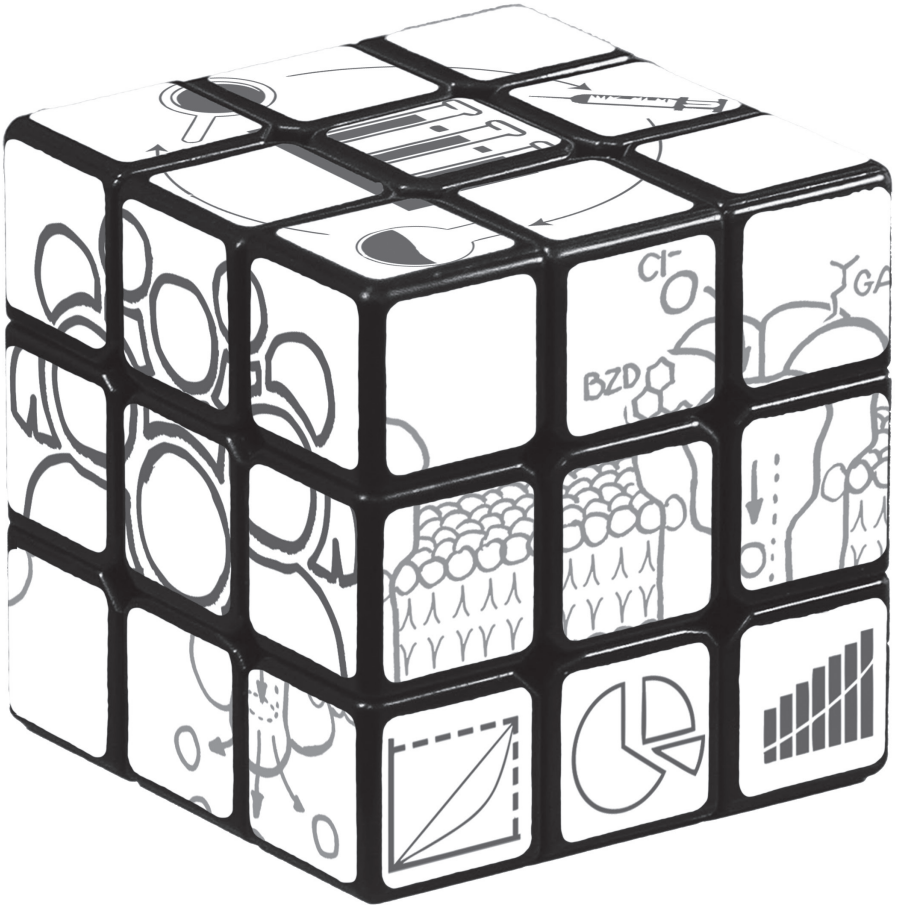
DISCUSSION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GENERAL DISCUSSION

CHAPTER 8

Day-case surgery is continuously progressing. Due to anesthetic and surgical advancements, outcome measurements have been shifted towards more patient centered outcomes like quality of recovery dominated by psychological phenomena. The aim of the present thesis was to evaluate the effectiveness of the most performed medical preparation prior to surgery (i.e. premedication) on these patient centered outcomes. Furthermore, in this thesis we attempted to identify vulnerable patients after day-case surgery according to these patient centered outcomes, and to give tools to predict them accurately which could lead to (more) tailored interventions. This chapter discusses the results together with its implications for clinical practice. Furthermore, future prospects will be outlined.

1.1 In retrospect

It was found that premedication with lorazepam was not strong enough to enhance quality of recovery and psychological phenomena including anxiety, feelings of fatigue, depression and aggression seven days after day-case surgery when compared to placebo. However, lorazepam might postpone the decrease in anxiety and aggression after day-case surgery (**Chapter 2**). An additional pharmacogenetic study showed that lorazepam premedication might be beneficial to some patient groups nonetheless. Particularly female patients with high preoperative anxiety scores might probably benefit from lorazepam premedication when they are homozygous carriers of the *UGT2B15*2* genotype (**Chapter 3**). On the other hand, systematic review and meta-analysis showed that psychological phenomena are not yet adequately addressed with regards to benzodiazepine premedication to date. Benzodiazepine premedication did show to have beneficial effects on postoperative side-effects such as nausea. Furthermore, time to discharge was not negatively affected after benzodiazepine premedication (**Chapter 4**).

Criteria for vulnerable patients were constructed. Subsequently, vulnerable patients were identified and predicted by means of prognostic modeling techniques (**Chapter 5 and 6**). It was found that roughly one third of the study population was vulnerable according to the constructed definition of vulnerability which was based on scores from the normal population (**Chapter 6**).

As the etiology of postoperative fatigue is still unknown, structural equation modeling was performed to take a first step in unravelling the preoperative and postoperative pathways between fatigue on the one hand and anxiety and depression on the other hand. Postoperative fatigue was predominantly induced by preoperative fatigue and, likely, not a consequence of anxiety and depression (**Chapter 7**).

1.1.1 Part 1: Premedication with lorazepam and other benzodiazepines

Randomized controlled clinical trials (RCTs) are, nowadays, the preferred method to evaluate the effectiveness of medical treatment. Researchers have critically discussed this framework however. Next to the time consuming efforts and costs, external validity is discussed in the literature.[1,2]

The Consolidated Standards of Reporting Trials (CONSORT) statement is mainly focussed on aspects that cover internal validation.[1,3] Although after the introduction of the CONSORT statement in 1996 trial reporting improved,[4,5] there are still trials published that lack providing important methodological content.[6] The performed RCT described in **Chapter 2** is in accordance with the CONSORT statement. Despite the fact that several modifications have been made over the years,[3,4,7] it still might benefit from further modifications. For example, treatment adherence is not specifically included in this checklist but is an important element of research quality.[8] The study by Zhang *et al* showed that treatment adherence is not always given in published RCTs which could lead to different interpretation of study results.[8] Previous RCTs in the field, i.e. testing benzodiazepine premedication, used oral dosages and lacked information about treatment adherence.[9-11] Also, the RCT described in **Chapter 2** did not report on treatment adherence. However, as the study medication was administered intravenously, treatment adherence equalled 100%.

Difficulties with internal validation will resonate in external validation. RCTs that are carried out at a single center – such as the one presented in this work – have less generalizability than multi-centered RCTs. Furthermore, patient selection creates a more homogeneous study population which limits generalizability too. In our case, Dutch patients with no history of preceding use of psychopharmaceuticals dominated the study population that might have biased the results of our patient related outcomes. However, still, external validity is a matter of judgement.[12]

The conclusions drawn from a single RCT should be interpreted cautiously as false negative results may be present.[12,13] A recent RCT in inpatient surgery also found no beneficial effect of lorazepam premedication on patient experience and patient quality of recovery at the first postoperative day.[14] Although that study did not evaluate lorazepam premedication beyond the first postoperative day like we did, the combined findings may suggest a lack of benefit with routine use of lorazepam as premedication. However, it might not be justified to withhold premedication routinely as it may be possible that subgroups of (vulnerable) patients could benefit from premedication. The relative wide confidence intervals of the outcome parameters in the presented RCT in

Chapter 2 might indicate a heterogeneous response to premedication with lorazepam. Meta-analysis of performed RCTs will give more robust results and therefore more firm conclusions.[12] However, it was not possible to make conclusive remarks with respect to the effectiveness of premedication with benzodiazepines on psychological outcome in our meta-analysis of RCTs in **Chapter 4.** Due to an insufficient number of trials examining the effect of benzodiazepines on psychological outcomes in day-case surgery, it was not allowed to make proper conclusions. With respect to postoperative side effects, we found beneficial results, and the results showed that time to discharge was not negatively affected after benzodiazepine premedication. Recently, two studies presenting systematic review and meta-analysis also showed a decrease in postoperative side-effects, i.c. post-operative nausea and vomiting.[15,16] These studies lacked the ability to generalize their results since they studied the perioperative use of midazolam only. Furthermore, the study population included mixed surgical patients. Nonetheless, available evidence increasingly suggests positive effects on post-operative side-effects without affecting time to discharge after premedication with benzodiazepines.

The main assumption made in the derived pharmacogenetic study, described in **Chapter 3**, included the achieved plasma level of lorazepam in patients. The rationale of this study was based upon previous profound research by Chung *et al* showing significant different plasma concentration of lorazepam according to *UGT2B15* genotype.[17] Thus, in our work, plasma levels of lorazepam were not assessed which makes the effect site concentration – effect relationship a matter of debate. The results of this study were complex: anxiety differences significantly depended on a highest order interaction between premedication (lorazepam yes/no), *UGT2B15* genotype status, patient gender, and preoperative level of anxiety. Although higher order interactions are mathematically correct, clinical interpretation is challenging as the outcome is explained by the combination of multiple variables. Visualisation can help the reader to understand the result, however sacrifices may be needed (i.c. dichotomization of a continuous variable). As significant lower order interactions are less relevant than higher order interactions,[18] higher order interactions should not be ignored for reasons of complexity.

1.1.2 Part 2: Identifying vulnerable patients

Prognostic modeling could facilitate health care professionals to aid medical decision making. We performed two studies using preoperative data in order to identify vulnerable patients in the postoperative period.

In **Chapter 5**, a prognostic model was constructed predicting multiple psychological outcomes simultaneously one week after day-case surgery. Clinically, a patient is more

than one outcome variable, especially when psychological phenomena are considered as outcome – these variables are likely intercorrelated. Statistically, when these outcomes are considered, the most appropriate and efficient way of analysing includes a joint analysis instead of running separate multivariable regressions. To achieve this, a structural equation modeling framework could be useful.[19] The constructed prognostic model (**Chapter 5**) showed substantial explained variances, but was still imperfect. Omitted and unknown variables could play a role, for example interpersonal variables. Model misspecification could have emerged. Furthermore, fallibility of the measurements is an option. We have refrained from correcting for measurement errors in the analyses, as this would make our study less suitable for use in clinical practice.

Although the scores of the psychological phenomena were not that high, sufficient variation c.q. heterogeneity was found. **Chapter 6** showed that 36% of our day-case surgery population was vulnerable after the surgery according to constructed cut-off scores (a patient was vulnerable when the score for an outcome exceeded one standard deviation above the mean according to normative scores). The creation of one single outcome including three vulnerability categories allowed us to use conventional statistical regression modeling (i.e. ordinal logistic regression modeling).[20] The proposed model showed a promising discriminative ability and model performance. Although the constructed composite scale (i.e. none-, single- and multiple vulnerable) enabled to classify patients for vulnerability and to predict them adequately, the costs for such a classification is loss of information.[20] The model selection was performed by backward elimination of determinants to find the most parsimonious model.[21] In our analysis strategy *P*-to-remove equalled 0.20. However others have used less stringent *P*-values especially in small data sets.[20,21] The latter strategy will allow more predictor variables in the final model.

In **Chapter 5** it is suggested that postoperative fatigue behaves differently when compared to the other psychological phenomena including anxiety, depression and aggression. This is imaginable as researchers have suggested several theories about the underlying causal structure. Some believe that the underlying structure is of somatic nature,[22] while others believe it should be explained in a psychological way.[23] Although the truth will lie somewhere in the middle,[24] the psychological theory of Salmon and Hall is still leading this field.[25-27] This theory states that anxiety and depression are misinterpreted as fatigue (i.e. somatisation) but the directionality assumed is never solved.[25,27] In **Chapter 7** a path analysis was executed to unravel directionality among these phenomena. Path modeling is a specific feature of structural equation modeling (SEM) which can be used to unravel directionalities of clinical pathways in complex

entities.[19,28] The most plausible model showed that fatigue likely induces anxiety and depression rather than vice versa. With regards to the theory of Salmon and Hall the difference could be explained by the medical context: day-case surgery patients are less hospitalised than the patients where the theory of Salmon and Hall is based on.

In this work SEM was performed on longitudinal data as well as on cross-sectional information, i.e. simultaneous measurements assessed at the same measurement moment. The temporal design in longitudinal data allows to make statistical judgement on directionality.[19] By definition temporal precedence cannot be demonstrated in cross-sectional data and inference about directionality is complicated therefore. However, SEM has also been performed on cross-sectional data to guide medical decision-making.[28,29] When study measures are assessed cross-sectionally and directionality is suggested, the researcher should provide a valid rationale.[19] Although the conclusion in **Chapter 7** is reluctant about directionality among fatigue, anxiety and depression when measured simultaneously, these pathways were presented in the model diagram as previous research has shown similar results with respect to these phenomena, and empirical tested therapies have directed into such a structure.[29,30]

Prior to the analysis there was no hypothetical construct concerning the direction of the pathways among fatigue, anxiety and depression within our day-case surgery study population. The three possibilities to deal with such a research question include defining a structural equation model without directionality, define and test all possible models, or include reciprocal effects in the defining model.[19] In the work presented all possible models were tested. As expected, equivalent models exist (i.e. different models fit the data structure equally well).[19] As we did not succeed to find a preferred pathway, it was decided to keep the pathways on the cross-sectional data similar (i.e. the preoperative and postoperative pathways were kept equal) as statistically it was not possible to choose one above the other. This limits claims about directionality. Causality (i.e. true directionality) can only be claimed when 1) the identified model is replicated in other independent study samples, 2) (near) equivalent models are definitely ruled out, and 3) empirical studies have demonstrated evidence for manipulable variables in the model and accurate prediction of effect of interventions.[19,31] These issues were beyond the scope of the current thesis and were not addressed therefore.

1.2 In prospect

Although there is variation in the progress of day-case surgery worldwide,[32] it has been estimated that 80% of elective surgical procedures will be carried out as day-case surgery.[33] In some parts of the world this percentage has already been achieved.[32] It

is expected that the increase of day-case surgery will continue since more and more complex surgical procedures are being carried out in a day-case setting. For example, craniotomies for brain tumour resection have recently been performed on a day-case base.[34,35] In addition, the worldwide population continues to expand together with aging.[36,37] As a consequence, the incidence of vulnerable patients undergoing day-case surgery will likely increase substantially. To preserve the medical and socio-economic success of day-case surgery, adequate care should be present for these vulnerable patients.

1.2.1 Part 1: Premedication with lorazepam and other benzodiazepines

To gain more insight in the role of lorazepam on psychological outcomes in the day-case surgery population, new randomized controlled clinical trials should be designed and conducted to improve generalizability. This is of incremental importance. It is widely known that the response to drugs can show wide variability among patients.[38] Including other biological-, cultural- and environmental factors will give more insight in possible variability in drug response.[38] Day-case surgery patients with other disease states such as abortion or brain tumour resection were not in the scope of this thesis. These patient groups could respond differently to premedication with lorazepam due to aberrant psychological and physiological processes altered by the underlying disease. With respect to cultural- and environmental factors, exploring lifestyle diversity could be of additional value. For example, the clearance of lorazepam – and other drugs primarily metabolized by uridine 5'-diphosphate-glucuronosyltransferases – has been found to be significantly higher in obese.[39,40]

Next to genetic factors affecting lorazepam metabolizing enzymes, the focus of future studies could also be the variability of lorazepam at the receptor site. Premedication (i.c. lorazepam) is regularly administered once, and, accordingly, the clinical effect is more dependent on the premedication distribution than on the premedication elimination.[41] The entry of drugs into the brain is controlled by the blood-brain-barrier (BBB) and the blood-cerebrospinal fluid barrier. Exploration of the latter is at a beginning stage.[42] Although several pathways exist for crossing the BBB, benzodiazepines cross the BBB predominantly via diffusion.[42,43] Furthermore, at the epithelial cells in the BBB, the apically located P-glycoprotein transporter controls drug entry over the BBB by pumping substrates out of cells.[44] P-glycoprotein is the most extensively studied active drug efflux transporter. One of the reasons for its popularity is the wide variety of substrates involved which also includes lorazepam.[42] Modifications in P-glycoprotein activity could probably result in different clinical effects of lorazepam premedication. On the one hand genetic disruptions such as gene polymorphisms are known that could affect

P-glycoprotein activity. For example, in 24% of the Caucasian population homozygosity occurs for an allele that is correlated with reduced P-glycoprotein activity.[45] On the other hand, chemical possibilities such as co-administration modifying P-glycoprotein activity could also be an option to investigate in order to obtain better therapeutic efficacy with lorazepam premedication. Literature shows heterogeneous results with respect to the effectiveness of co-administration that is able to inhibit P-glycoprotein (e.g. quinidine),[46-48] i.e. co-administration does not always provide the expected enhanced effect of drugs that are P-glycoprotein substrates. One of the hypotheses includes the role of lipophility of the drug. It is suggested that the more lipophilic the drug, the less pronounced efflux via P-glycoprotein.[42,49] This should be taken into account when co-administration modifying P-glycoprotein is considered. Among the benzodiazepines, lorazepam has a moderate lipophility.[50,51]

Another way to improve the clinical efficacy of lorazepam premedication is to improve its affinity to the $GABA_A$ receptor complex after its entrance to the CNS. Several modifications in the $GABA_A$ receptor have shown interesting results with respect to benzodiazepine sensitivity.[52-55] It remains to be explored whether these modifications can be applied to lorazepam.

Future studies could also analyse other benzodiazepines as premedication prior to day-case surgery. In accordance with the aging population it is advised to administer benzodiazepines that undergo Phase II metabolism only such as oxazepam and temazepam, as these have no active metabolites and substantial drug interactions are rare.[42] Furthermore, administration of benzodiazepine premedication should be considered carefully since it is known that it also may cause, for example, agitation and delirium.[56-58] The most optimal (benzodiazepine) premedication will likely be different for different sets of (vulnerable) patients.

1.2.2 Part 2: Identifying vulnerable patients

In this thesis the focus was on the relationships among variables by using a variable centered approach. Adding statistical methodologies that take into account a patient-centered approach could be helpful to identify vulnerable patients in the growing heterogeneous day-case surgery population – more elderly, and more complex surgery will be more and more exposed to day-case surgery in the near future. Such statistical methodology aims to group (non) vulnerable patients into various sets of patients that each have their own unique characteristics. Thus, the focus here is on relationships among patients.[59] A couple of the most used methods that integrate variable-centered and person-centered include latent class analysis, latent transition analysis, latent class

growth analysis, and (general) growth mixture modeling. The description and purpose of these statistical methodologies are well described elsewhere.[59] Thus, in short, these methods try to cluster patients from a heterogeneous population into (latent) classes that represent a homogeneous subpopulation that has its own set of parameter values.[59] This may enable a tailored treatment approach to such a subpopulation.

Furthermore, in addition to well-known model modifications in prognostic modeling such as including other determinants and replication of the model in other sets of patients,[20] prognostic modeling in day-case surgery patients could especially benefit from additional measurement moments. For example, adding distal outcomes (i.e. long term outcomes) that cover rehabilitation success such as returning to normal daily activities, returning to work, etcetera. Multiple preoperative measurements would also help to understand the preoperative period in (vulnerable) patients and to create more time for appropriate interventions if needed. More preoperative and postoperative measurements will also help to confirm the direction of the pathways between fatigue on the one hand and anxiety and depression on the other hand. If future research could confirm the found perioperative pathway from fatigue to anxiety and depression (**Chapter 7**), prognostic studies could be simplified according to parsimonious modeling by focussing particularly on reducing preoperative fatigue.

The definition of a vulnerable patient is a matter of judgement. Therefore we have chosen to create and validate a prognostic model that was not restricted to a cutoff point of vulnerability (**Chapter 5**). Subsequently, the vulnerability threshold of an individual patient is for the discretion of the health care professional. Many criteria could be used. One possibility is described in **Chapter 6**: a patient is considered vulnerable when the score is more than one standard deviation away from the mean according to the normal population. Subsequently, decision making with respect to treatment options for these vulnerable patients becomes feasible.

Further studies could be subjected to evaluate different decision rules in combination with possible treatments. In day-case surgery, decision rules that take into account multiple outcomes seem indicated. Some methods that may be of interest are well described elsewhere.[60,61] When decision rules are validated they might be incorporated in expert (critiquing) systems. These systems provide a computer-based advice to the physician for clinical decision making.[62] Such a computer program was previously applied in anesthesiology for risk assessment.[62] Although the clinical utility needs further exploration, these programs have shown potential as a tool for prevention.[63]
The decision to offer a vulnerable patient a treatment, and especially which kind of

treatment is of particular clinical interest but still not investigated in day-case surgery patients. According to the identified vulnerable patients in **Chapter 6**, it is likely that single vulnerable patients need a different treatment plan than multiple vulnerable patients.

Intervening preoperatively is currently of increasing interest. Synthesis of evidence has shown promising results on postoperative outcomes.[64] These programs are called 'prehabilitation programs'. These programs seem superior to rehabilitation programs – programs that intervene in the postoperative period, especially when they use a multimodal framework.[64] The prehabilitation time frame in day-case surgery includes the preoperative period from the moment of the medical diagnosis until the moment of the surgical intervention. Since the surgical procedures are electively planned in day-case surgery, a prehabilitation program should be able to perform. Moreover, the study presented in **Chapter 6** showed that one-third of our day-case population show vulnerable features with respect to psychological outcome parameters showing the need to improve these postoperative outcomes. Nevertheless, currently, no evidence-based prehabilitation program – or rehabilitation program or a combination of the two – does exist for the day-case surgery population. But, if a prehabilitation program is desired, who will lead its development, implementation, and evaluation? Since multimodal prehabilitation programs focussing on physical, nutritional and psychological aspects seem more effective,[64,65] a multidisciplinary team including, for example, the anesthesiologist, the surgeon and the psychologist will be needed. Furthermore, it is likely that a beneficial and cost-effective prehabilitation program in day-case surgery may differ according to the postoperative outcomes of interest and health care settings.[66] For example, if reducing postoperative fatigue is intended, it might be reasonable to focus on reducing preoperative fatigue as this might lower fatigue, anxiety and depression postoperatively (**Chapter 7**). Subsequently, for example, the constructed prediction models in the current thesis may not fully apply and new prediction models tailored to preoperative fatigue need to be designed by statisticians. Furthermore, treatment options will likely change and more tailored to the primary phenomenon. In the case of fatigue, psychological relaxation therapies and cognitive behavioural therapy have shown potential in reducing fatigue.[67,68] Accordingly, psychological professionals are needed to perform or teach these treatments which should be evaluated in well-conducted studies. When the objective is to adjust patients' lifestyle to reduce body weight to make, for example, lorazepam premedication more effective, a dietician and/or physiotherapist is likely desired.

So, who should coordinate a prehabilitation program in day-case surgery in order

to prevent vulnerability after surgery? I would suggest the anesthesiologist. Risk assessment and managing multidisciplinary teams perioperatively are skills that are predominantly dedicated to anesthesiologists.[69,70] Furthermore, it was previously recommended that, in day-case surgery, "anesthesiologists should take the lead in studying the impact of post discharge symptoms and advocating for our patient's best care, even if it involves care beyond our traditional period of involvement".[71] However, as the daily clinical practice of a medical doctor is quite busy, tasks may be delegated to trained and dedicated day-case surgery nurses as soon as their role is well described in protocols. This corresponds with the concept of the start of day-case surgery, more than a 100 years ago.[72,73]

1.3 Concluding remarks

This thesis aimed to evaluate the effects of premedication with benzodiazepines, in particular lorazepam, on the quality of recovery of day-case surgery which is dominated by psychological outcome parameters nowadays. The studies reveal that, in general, patients undergoing day-case surgery have no additional benefit with benzodiazepine premedication with respect to these outcome parameters, although future studies are needed to make more firm conclusions. The studies also reveal that lorazepam premedication might be beneficial in subgroups of day-case surgery patients. Furthermore, benzodiazepine premedication has beneficial effects on postoperative side-effects and does not negatively affect time to discharge. This thesis also illustrates that the application of novel statistical methodologies can help in unravelling the pathways among variables, and can lead to adequate identification of vulnerable patients paving the way for optimal medical decision making in day-case surgery.

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APPENDICES

SUMMARY

Chapter 1 is a general introduction about the concept of day-case surgery, the preoperative evaluation, and possible preparation of patients for the surgical procedure with specific attention to premedication with benzodiazepines, in particular lorazepam. Furthermore, postoperative evaluation and statistical modeling is outlined.

Chapter 2 presents a randomized placebo controlled clinical trial that was undertaken to assess the effectiveness of premedication with lorazepam on the quality of recovery and psychological phenomena including anxiety, feelings of fatigue, depression and aggression up to seven days after day-case surgery. The results showed that premedication with lorazepam did not improve quality of recovery. Furthermore, it was found that the postoperative decrease in anxiety was lower in the lorazepam group, and that the postoperative aggression scores were slightly increased in this group.

Chapter 3 concerns a derived pharmacogenetic study evaluating patient variability in anxiolytic effect after premedication with lorazepam according to the *UGT2B15* genotype. It was found that the *UGT2B15* genotype polymorphism influences postoperative anxiety levels. This clinical effect was also depended on the interaction with patient gender and the preoperative anxiety score. Further exploration showed that high preoperative anxious females with genetically reduced lorazepam glucuronidation (*UGT2B15*2* homozygotes) had more anxiety reduction than males with the same genotype.

Chapter 4 reviews the effectiveness of premedication with benzodiazepines on postoperative somatic symptoms/complaints and psychological phenomena in day-case surgery by means of a systematic literature review with meta-analysis of randomized placebo controlled clinical trials. Benzodiazepines showed to have favourable effects on postoperative somatic symptoms/complaints such as nausea. Regarding psychological phenomena, only anxiety could be subjected to meta-analysis showing no statistical difference. More research is needed to make firm conclusions on psychological outcomes. Furthermore, this review concluded that the reluctance of some anesthesiologists to administer benzodiazepine premedication in day-case setting is not justified for reasons of delayed recovery – time to discharge was not negatively affect after benzodiazepine premedication.

Chapter 5 describes the results of a prognostic model using preoperative data including sociodemographic, medial and psychological determinants in order to predict multiple psychological outcomes jointly one week after day-case surgery. Apart from state aggression the psychological outcomes could be adequately predicted using the

identified model. Sociodemographic and medical variables were of minor importance, with the exception of gender and having children. In contrast, the psychological variables as assessed at baseline were of prominent importance.

Chapter 6 defines a definition of a vulnerable patient with respect to psychological outcomes one week after the surgical procedure based on scores from the normal population. Roughly one third of the study population was identified as being vulnerable. Subsequently, a prediction model was constructed using preoperative data that was able to predict adequately vulnerability in day-case surgery patients.

Chapter 7 describes a study aimed to unravel potential pathways leading to postoperative fatigue based on a theory assuming that anxiety and depression are closely related to fatigue. Using a structural equation modeling framework, it was suggested that postoperative fatigue is likely induced via preoperative fatigue and not a consequence of anxiety and depression.

Chapter 8 includes the general discussion. The results and methodological considerations of this thesis are discussed. Furthermore, clinical implications and recommendations for future research are given.

SAMENVATTING

Hoofdstuk 1 is een algemene introductie over het concept van operaties in dagbehandeling. De preoperatieve evaluatie en mogelijke voorbereidingen voor patiënten met betrekking tot de chirurgische ingreep worden besproken. De aandacht gaat hierbij uit naar premedicatie met benzodiazepines, in het bijzonder lorazepam. Verder is de postoperatieve evaluatie en het statistisch modelleren uiteengezet.

Hoofdstuk 2 betreft een gerandomiseerde placebo gecontroleerde klinische trial dat was uitgevoerd om de effectiviteit van premedicatie met lorazepam te meten tot zeven dagen na de operatie op de kwaliteit van het herstel en op de volgende psychologische verschijnselen: angst, gevoelens van vermoeidheid, depressie en agressie. De resultaten toonden aan dat premedicatie met lorazepam niet de kwaliteit van het herstel verbeterde. Tevens bleek dat de postoperatieve angstreductie lager was in de lorazepam groep en dat de postoperatieve agressiescores subtiel waren toegenomen in deze groep.

Hoofdstuk 3 betreft een afgeleide farmacogenetische studie dat de variabiliteit tussen patiënten in anxiolytisch effect na premedicatie met lorazepam evalueerde met betrekking tot het *UGT2B15* genotype. Het bleek dat het *UGT2B15* genotype polymorfisme de postoperatieve angstscores beïnvloedde. Het klinische effect hing ook af van de interactie tussen het geslacht van de patiënt en de preoperatieve angstscore. Verdere exploratie toonde aan dat preoperatief hoog angstige vrouwen met genetisch gereduceerde lorazepam glucuronidatie (*UGT2B15*2* homozygoten) meer angstreductie hadden dan mannen met hetzelfde genotype.

Hoofdstuk 4 bespreekt de effectiviteit van premedicatie met benzodiazepines op postoperatieve somatische symptomen/klachten en psychologische verschijnselen bij operaties in dagbehandeling door middel van een systematische literatuurstudie en meta-analsye van gerandomiseerde placebo gecontroleerde klinische trials. Benzodiazepines bleken gunstige effecten te hebben op postoperatieve somatische symptomen/klachten zoals misselijkheid. Met betrekking tot de psychologische verschijnselen was het enkel mogelijk om angst te onderzoeken in een meta-analyse. Er bleek geen statisch verschil te zijn. Meer onderzoek is nodig om meer gefundeerde conclusies te trekken over psychologische uitkomstmaten. Verder concludeerde deze literatuurstudie dat de terughoudendheid van sommige anesthesiologen om premedicatie met benzodiazepines toe te dienen bij operaties in dagbehandeling niet gerechtvaardigd is op basis van gedachten dat dit een vertraagd herstel geeft – het tijdstip van ontslag werd niet negatief beïnvloed na premedicatie met een benzodiazepine.

Hoofdstuk 5 beschrijft de resultaten van een prognostisch model dat gebruik maakte van preoperatieve data welke bestond uit sociodemografische, medische en psychologische determinanten om zo meerdere psychologische uitkomstmaten, die een week na de operatie in dagbehandeling waren gemeten, gezamelijk te voorspellen. Behalve de situationele agressie konden de psychologische uitkomstmaten goed worden voorspeld wanneer gebruik werd gemaakt van het geïndentificeerde model. Met uitzondering van geslacht en het al dan niet hebben van kinderen waren de sociaaldemografische en medische variabelen van ondergeschikt belang. De psychologische variabelen die op baseline werden gemeten, waren daarentegen van prominent belang.

Hoofdstuk 6 geeft een definitie van een kwetsbare patiënt met betrekking tot psychologische uitkomsten een week na de operatie in dagbehandeling. Dit was gebaseerd was op scores van de normale populatie. Ongeveer een derde van de studiepopulatie werd geïndentificeerd als kwetsbaar. Vervolgens werd op basis van preoperatieve data een voorspellend model geconstrueerd dat in staat was om op een adequate manier de kwetsbaarheid van deze patiënten te voorspellen.

Hoofdstuk 7 beschrijft een studie die gericht was op het ontrafelen van potentiële paden die leiden naar postoperatieve vermoeidheid. De studie was gebaseerd op een theorie die ervan uitgaat dat angst en depressie nauw verwant zijn met vermoeidheid. Met behulp van een *Structural Equation Modelling* framework werd gesuggereerd dat postoperatieve vermoeidheid waarschijnlijk geïnduceerd wordt via preoperatieve vermoeidheid en dat dit niet een gevolg is van angst of depressie.

Hoofdstuk 8 bevat de algemene discussie. De resultaten en methodologische overwegingen van dit proefschrift worden bediscussieerd. Verder worden klinische implicaties en aanbevelingen voor verder onderzoek gegeven.

DANKWOORD

Tijdens mijn studie geneeskunde raakte ik al snel klinisch betrokken bij de afdeling anesthesiologie. Naast mijn studie wilde ik mij ook graag op wetenschappelijk gebied ontwikkelen. Toen ik, in het kader van de master Clinical Research, de mogelijkheid kreeg om, op dezelfde afdeling anesthesiologie, een gerandomiseerd, dubbelblind, placebo-gecontroleerd onderzoek op te zetten en uit te voeren, heb ik geen moment getwijfeld om dit project te starten. Ik wist destijds nog niet dat het zou uitgroeien tot een promotietraject. Ik ben altijd vastberaden geweest om dit project van het begin tot en met het einde te voltooien. Ik ben zeer dankbaar dat ik door dit proces heb mogen gaan. Vele mensen zijn op mijn pad gekomen en hebben mij hierin geholpen. Dit proefschrift is daarom niet compleet zonder dankwoord en daar wil ik dan ook graag mee besluiten.

Allereerst mijn promotor, **prof. dr. R.J. Stolker**. Het project was al enige tijd aan de gang toen ik voor het eerst een 'officiële' afspraak met u had. Naast het feit dat het gesprek zeer informatief en opbouwend was, was het ook gezellig. Ik vond het bijzonder dat u alle tijd voor mij nam. Echter dit bleek geen uitzondering te zijn, want op alle afspraken die volgden nam u uitgebreid de tijd om mijn werk te bespreken. Altijd lagen mijn stukken al klaar, volledig voorzien van correcties, suggesties en overige feedback. Ik kreeg van u veel vrijheid om mijn gedachten te verwerken. U overwoog ze grondig en schaafde ze bij waardoor ik in de juiste richting bleef gaan. U was altijd positief, gaf perspectief en motiveerde enorm als het tegen zat. Het feit dat u een zeer gepassioneerde en betrokken promotor bent, werd nog maar eens duidelijk toen u uitgebreid participeerde in het analyseren van de studies voor het systematische review met meta-analyse. Daarnaast bent u altijd de spin in het web geweest in deze multidisciplinaire onderzoeksgroep. Dank ook voor het feit dat u betrokken wilt zijn in het verwezenlijken van mijn klinische ambitie. Ik hoop van harte dat we in de toekomst op zowel persoonlijk als op professioneel vlak contact zullen blijven houden. Ik vind het een eer om bij u te mogen promoveren.

Copromotor, **dr. M. Klimek**. Als ik terugkijk is het erg bijzonder om te zien wat voor weg wij hebben gelopen. Na één meeloopdag op de OK nodigde u mij uit om te solliciteren in het PACU studententeam, waar ik jaren met zeer veel plezier heb mogen werken. Daarnaast gaf u mij de mogelijkheid om een RCT op te zetten en uit te voeren onder uw directe supervisie. Ik ben u hier buitengewoon dankbaar voor. U gaf me veel ruimte om mijzelf te ontplooien en voorzag mij van alle faciliteiten om onderzoek te kunnen doen. U was altijd bereikbaar en gaf gevraagd en ongevraagd waardevolle adviezen. Daarnaast stond u mij altijd direct bij op de 'werkvloer' als dat nodig was. Van dichtbij heb ik mogen leren van uw klinisch en wetenschappelijk redeneren en het omgaan

met en oplossen van tegenslagen. Onder andere door uw mentorschap heb ik een MSc in Clinical Research en KNAW Akademie Assistentschap succesvol kunnen afronden waar ik u tot op de dag van vandaag dankbaar voor ben. Uw betrokkenheid was verder zichtbaar door het feit dat u bij iedere presentatie van het onderzoek aanwezig was. Dank dat u altijd bereid bent om mee te denken en te helpen mijn klinische carriere vorm te geven. Daarnaast waardeer ik ook de vriendschap buiten de werksfeer en hoop deze nog lang te kunnen onderhouden.

Copromotor, **dr. H.J. Duivenvoorden**. Ik ben zeer dankbaar dat u één van mijn leermeesters bent geworden. Tijdens onze eerste afspraken over het opzetten van de RCT bleek – achteraf gezien – al dat u een ras wetenschapper bent. U trok het onderzoek in een breder perspectief en stippelde al snel een promotie-traject uit, wat uiteindelijk mede heeft geleid tot dit huidige werk. Ik kon toen nog niet voorzien hoe belangrijk u was voor de fundering en uitvoering van dit project. Op vele gebieden heb ik ongekend veel van u mogen leren, in het bijzonder over methodologie en het bedenken en uitvoeren van statistische analyses. Ontelbare keren bent u naar de onderzoekskamer afgereisd om samen met mij data te analyseren, ideeën uit te werken, al mijn vragen te beantwoorden en ga zo maar door. Dat u een ras wetenschapper bent bleek nog maar eens toen u na uw pensioen gewoon door wilde gaan met het begeleiden van het onderzoek. Ik bewonder uw wetenschapsfilosofie. Uitspraken als "houd het simpel, maar niet simplistisch" en "de patiënt is meer dan een uitkomstvariabele" zullen mij altijd bijblijven. Graag wil ik u ook bedanken voor uw persoonlijke adviezen omtrent het begrenzen van onderzoek in mijn privéleven. Ik hoop met u dit goede contact te kunnen onderhouden.

Prof. dr. E.W. Steyerberg, prof. dr. T. van Gelder en **prof. dr. L.P.H.J. Aarts**, dank voor uw bereidheid om plaats te nemen in de leescommissie en zo dit proefschrift op zijn wetenschappelijke waarde te beoordelen. **Prof. dr. E.W. Steyerberg** dank voor uw coaching en stimulatie gedurende een deel van dit project. Ik kon altijd laagdrempelig bij u aankloppen voor vragen.

Prof. dr. H.J.M. Verhagen, prof. dr. J. Passchier en **prof. dr. B. Preckel**, dank voor uw bereidheid om in de grote commissie plaats te nemen om van gedachten te willen wisselen over de inhoud van mijn proefschrift.

Het personeel van de **chirurgische dagbehandeling van het Erasmus MC** onder leiding van **Joleen Smit** wil ik bedanken voor de bereidheid om mee te werken met dit project. Zonder jullie welwillendheid had dit project nooit uitgevoerd kunnen worden.

In het bijzonder wil ik **Jeanette den Hollander** en **Henk van Welzen** bedanken. Jullie waren mijn steun en toeverlaat op respectievelijk de verpleegafdeling en de preoperatieve holding van de chirurgische dagbehandeling. Door jullie enthousiasme en gedrevenheid heeft het onderzoek op de juiste manier kunnen plaatsvinden. Dank voor het meedenken en de vele gouden tips op de afdeling. Daarnaast waren de wedstrijden naar SPARTA Rotterdam altijd bijzonder gezellig.

Stefan van Beek, collega, zwager en vriend. In het begin heb ik getwijfeld om je te betrekken bij de PACU en bij dit project, gezien onze familieband. Echter toen ik de knoop had doorgehakt, heb ik nooit meer getwijfeld. We kunnen goed privé en werk gescheiden houden en het is soms juist prettig om korte lijntjes te hebben. Je bent bereid om hard te werken en hebt goede ideeën. We kunnen goed gestructureerd samenwerken en mede daarom is de RCT goed verlopen. Het is mooi om te zien dat het vervolg op dit project onder jouw hoede valt en ik ben blij dat ik je hier bij kan helpen. Ik hoop dat we in de toekomst nog veel samen mogen werken! Ik ben dankbaar dat je mijn zwager én paranimf bent.

Ko Hagoort, bedankt voor uw tijd in het reviewen van de eerste manuscripten en presentaties op de Engelse taal.

Een aantal mensen hebben een specifiek deel van dit project mogelijk gemaakt. **Prof. dr. Ron van Schaik** wil ik bedanken voor het mogelijk maken en het faciliteren van de analyses naar het *UGT2B15* genotype. Tevens wil ik u danken voor uw wetenschappelijke bijdrage aan het desbetreffende manuscript. Ik dank **dr. Frank Grüne** voor de hulp bij het opzetten van dit project en de gezellige doch informatieve ontmoetingen in de wandelgangen. **Drs. Esther Pluijms** wil ik bedanken voor het bereid zijn voor het vervullen van de functie onafhankelijke arts voor patiënten als zij vragen hadden over dit project. **Wichor Bramer** ben ik veel dank verschuldigd voor de hulp bij het vinden van de juiste literatuur voor de systematische review en meta-analyse. **Daan Nieboer** dank ik voor de hulp bij statistische analyses in het programma *R*.

Bart ten Brinke, bedankt dat je op deze bijzondere dag naast me wilt staan als paranimf. Het voelt goed dat je naast me staat gezien onze vriendschap die we sinds de aanvang van de studie geneeskunde hebben. De mooiste periode was ongetwijfeld de jaren dat we huisgenoten waren. Je had altijd tijd voor een 'bakkie' en een goed gesprek over de zin en onzin van het leven. Ik wens je veel succes met je opleiding tot orthopeed.

Maarten voor de Poorte, Mr. Artist, we kennen elkaar al jaren en hebben al veel samen

meegemaakt. Het is nooit saai dankzij jouw creatieve brein. Gaaf dat je de cover en de covers van de hoofdstukken – en het verhaal erachter – hebt willen ontwerpen. De cover heeft, nu jij hem hebt ontworpen, voor mij een extra dimensie. De vele telefoontjes hierover mag je bij mij declareren.

Mijn familie wil ik graag bedanken. Mijn broer **Matteo** en zussen **Margrit** & **Antoinet** dank ik voor de warme band die we samen hebben. Als 'oudste broer' ben ik hier erg blij mee. In het bijzonder wil ik mijn ouders noemen. Jullie weten als geen ander wat dit project allemaal heeft gekost. Lieve **ma**, van jongs af aan heeft u alles op zij gezet voor ons en voor mij. Altijd was u voor ons thuis en creeërde u rust zodat een ieder thuis kon studeren. U cijferde zichzelf altijd weg en plaatste ons in het middelpunt – bewonderingswaardig. Dank voor al uw support. Beste **pa**, dank voor de bijzondere relatie die we hebben. We kunnen erg goed samen praten en werken. Dank voor de vele gesprekken en vaderlijke adviezen als ik ergens tegen op zag of wat dan ook. Uw christelijke kaders zijn mij altijd tot steun en helpen mij om verder te gaan.

Als laatste wil ik mijn lieve vrouw, **Marieke**, bedanken voor haar onvoorwaardelijke steun tijdens deze periode. We leerden elkaar kennen toen dit project net was gestart. Zoals je hebt gemerkt was dit project voor mij niet altijd een makkelijke periode en voor jou een belasting die je er gratis bij kreeg. Als gevolg wilde je eigenlijk pas trouwen als "dat onderzoek" allemaal achter de rug was. Gelukkig trouwden we eerder en zijn we al weer twee jaar gelukkig getrouwd. Dankzij jou heb ik de moed erin gehouden. Jouw positieve karakter, scherpe blik, relativeringsvermogen en praktische hulp zijn leidend geweest in de voltooiing van dit proefschrift. Je bent zonder meer het beste wat mij is overkomen.

CURRICULUM VITAE

Hendrik-Jan (Herjan) Mijderwijk was born on December 22nd, 1988 in Driebruggen, the Netherlands. After graduating from secondary school (Gymnasium, Nature&Health, Willem van Oranje College, Waalwijk) in 2007, he started his medical training at the Erasmus University Medical Center in Rotterdam. Next to following the ordinary study of medicine, he also started a Master of Science (MSc) program in Clinical Research at the Netherlands Institute of Health Sciences in 2009. During this program he received training particularly in epidemiology and biostatistics. In 2011 he attended the Graduate Summer Institute of Epidemiology and Biostatistics at the Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA. In the context of his MSc he started with the design and conduction of a Randomized Placebo Controlled Clinical Trial at the Day-Case Surgery department of the Erasmus MC in close collaboration and under the supervision of Prof. dr. R.J. Stolker, dr. M. Klimek, and dr. H.J. Duivenvoorden. Data collection and data analysis from patients treated at the Day-Case Surgery department formed the basis of the current thesis. In 2012 an MSc degree in Clinical Research was obtained. He was awarded a Royal Netherlands Academy of Arts and Sciences (KNAW) Academy Assistantship and a KNAW Research Traffic Grant for his scientific work. The latter was used, together with a grant from the Stichting Prof. Michael-van Vloten Fonds, for a clinical neurosurgical internship at the National Hospital for Neurology and Neurosurgery, London, UK in 2014. Subsequently, in the same year, he obtained *cum laude* his medical degree. From that point on he works as a medical doctor aiming for a training position in Neurosurgery. He became a registered epidemiologist in 2015. Besides his medical studies and work he continued his scientific research that has led to this PhD candidacy and this thesis entitled: Medical Decision Making in Day-Case Surgery.

PHD-PORTFOLIO

Name PhD Student	Hendrik-Jan (Herjan) Mijderwijk
Department	Anesthesiology
Research School	Cardiovascular Research School Erasmus University Rotterdam
Title Thesis	Medical Decision Making in Day-Case Surgery
Promotor	Prof. dr. R.J. Stolker
Copromotoren	Dr. H.J. Duivenvoorden; Dr. M. Klimek
Date of thesis defence	December 14, 2016

ACADEMIC EDUCATION & DEGREES

2015	Registered Epidemiologist (A)
2011 – 2014	Medical Doctor / Artsdiploma *cum laude* Erasmus Medical Center, Rotterdam, The Netherlands
2009 – 2012	MSc Clinical Research Netherlands Institute of Health Sciences, Rotterdam, The Netherlands
2007 – 2011	Doctorate in Medicine Erasmus Medical Center, Rotterdam, The Netherlands

PRESENTATIONS, CONFERENCES, PEER-REVIEWING

2016	"Wetenschapsdag" Anesthesiology, e-poster presentation
2014	Peer Reviewer for Anxiety, Stress, & Coping - An International Journal
2014	"Wetenschapsdag" Anesthesiology, oral presentation
2013	8th Invitational Conference Benchmarking OK, poster presentation
2012	Nederlandse Anesthesiologen dagen, oral presentation
2011	KNAW symposium, oral presentation
2009 – 2012	Several oral presentations regarding the research project

GRANTS & AWARDS

2011	Royal Netherlands Academy of Arts and Sciences (KNAW) Research Traffic Grant
2010 – 2011	KNAW Academy Assistantship

TEACHING ACTIVITIES

2015 – 2016	Docent Erasmus Medical Center Tutor second year medical students
2014 – 2015	Docent Erasmus Medical Center Tutor first year medical students
2010 – present	Supervising MSc/PhD Student, Stefan van Beek

MSc CLINICAL RESEARCH (2009-2012)

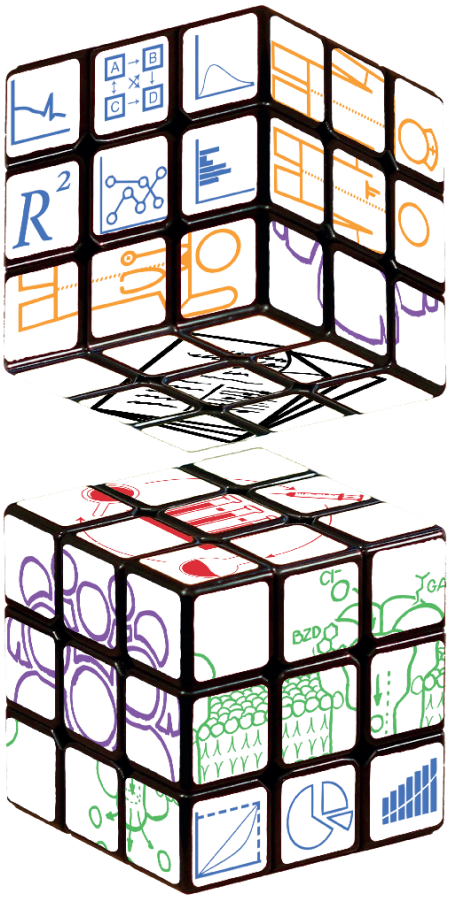
COURSE TYPE	*COURSE*	*ECTS*
Erasmus Summer	Principles of Research in Medicine and Epidemiology	0.7
Programme	Introduction to Data-analysis	1.0
	Regression Analysis	1.9
	Methods of Clinical Research	0.7
	Methods of Public Health Research	0.7
	Clinical Trials	0.7
	Topics in Meta-analysis	0.7
	Pharmaco-epidemiology	0.7
	Survival Analysis	1.9
	Cohort Studies	0.7
	Introduction to Decision Making in	0.7
	Medicine Markers and Prognostic Research	0.7
Core Courses	Study Design	4.3
Specific Course	Broad Orientation – medical study (broad)	5.0

Advanced Courses	Repeated Measurements in Clinical Studies	1.4
	Courses for the Quantitative Researcher	1.4
	Introduction to Clinical Research	0.9
	Advanced Topics in Decision - Making in Medicine	1.9
	Pharmaco-epidemiology and Drug Safety	1.9
	Intervention Research and Clinical Trials	0.9
	Diagnostic Research	1.1
	Advanced Topics in Clinical Trials	1.9
	Advanced Analysis of Prognosis Studies	0.9
	Prognosis Research	0.2
	Principles of Epidemiologic Data - Analysis	0.7
	Research Seminars 1	3.0
	Research Seminars 2	3.0
	Summercourses at Johns Hopkins (USA)	4.2
Skill Courses	Working SPSS for Windows	0.15
	A First Glance at SPSS for Windows	0.15
	Scientific Writing in English for Publication	2.0
Research	Development Research Proposal	11.0
	Oral Research Presentation	1.4
	Research Period	60.3
	Research Symposium	1.4
TOTAL		*120.2*

OTHER

2015	Re-certification Basiscursus Regelgeving en Organisatie voor KlinischOnderzoekers (BROK)
2011	BROK
2010-2011	KNAW lectures

DE COVER



De cover toont een onopgeloste Rubik's Cube toegepast op dit proefschrift. Wetenschappelijk onderzoek begint met een onopgelost vraagstuk. Om tot een oplossing te komen moet er, net als bij een Rubik's Cube, veel worden gepoogd, gewikt en gewogen. Perspectieven kunnen gaandeweg veranderen. Soms moet worden teruggedraaid om een andere route in te slaan. Eén passende zijde leidt nog niet tot een opgeloste Rubik's Cube. De oplossing van een wetenschappelijk vraagstuk vereist vaak ook een passende multidimensionale benadering. De toegepaste Rubik's Cube in dit proefschrift bevat zes afbeeldingen die de inhoud van het proefschrift representeren. Aan het begin staan alle zijden nog door elkaar. Echter, gedurende het project wordt steeds duidelijker hoe de hoofdstukken zich tot elkaar verhouden. De Rubik's Cube lost zich meer en meer op, maar is bewust nog niet voltooid. Dit proefschrift is dan afgerond, de volledige oplossing is nog niet daar. Gelukkig, want:

It is not knowledge, but the act of learning,
not possession but the act of getting there,
which grants the greatest enjoyment.

- Carl Friedrich Gauss (1777 - 1855)

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