

# **Pharmacological Interventions to Reduce Preoperative Anxiety among Patients with Major Surgery**

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## **Abstract**

**Introduction:** Stress and anxiety are negative feelings which can antagonistically impact the surgical outcomes and additionally influence the patient's recovery. This review aimed to summarize the pharmacological interventions used to control of preoperative anxiety.

**Methods:** An electronic search in MEDLINE and EMBASE was done using a combination of keywords. The search resulted in 64 studies, which were screened for eligibility criteria such as clinical trial design, English language, and human studies. After exclusion of ineligible, duplicated and review studies, the full text of the eligible studies were screened and the data were extracted. The characteristics for which data were collected included sample size, age of patients, type of surgery, medications used to reduce anxiety, dose and regime of medications, effect of reduction in anxiety. The findings of the review summarized in table of inclusion studies.

**Results:** The search of the literature, after exclusion of ineligible studies, revealed 14 studies met the inclusion criteria. Included studies aimed to investigate, from randomized controlled trials, the pharmacological interventions for control of preoperative anxiety. The total number of included patients was 983, of them adult subjects was 556 with the age range of 18-70 years and 427 children with the age range of 1-11 years. Some of the included placebo-controlled trial while active control were recruited in other studies. Regarding the main outcome which is the reduction of preoperative analgesia reported in many included studies while no difference appeared in other studies.

**Conclusions:** Benzodiazepines remain the medication of choice for the treatment of preoperative anxiety. However, many cautions should be taken in using preoperative medications among specific groups of patients such as hypersensitive reaction or physical dependence on the prescription.

**Keywords:** Anxiety, Stress, Fear, Therapy, Surgery.

## Introduction

Stress and anxiety are negative feelings which can antagonistically impact the surgical outcomes and additionally influence the patient's recovery. Other drawbacks included, difficulty in application of intravenous catheter in the preoperative stage as a result of stress vasoconstriction [1]. Additionally, anxious patients responded differently to the anesthesia [2] where higher doses are required to achieve an adequate anesthesia. Although a sedative medication is much of the time given as premedication to lessen fear and strain, tense patients may benefit by education from the anesthesiologist. However, in clinical practice, the anesthesiologist has no time for preoperative reassurance for the anxious patients [3].

Concerning pharmacological approach, the utilization of medication for the management of preoperative anxiety in adults and children has been studied by several studies. Midazolam is the most routinely used opiate prescription as premedication in children [4]. Preoperative medications have been credited several advantages such as reduce amount of anesthesia, anxiolysis and fast onset of sedation [5]. On the other hand, premedication with clonidine, but less significantly, has been appeared to constantly convey preoperative sedation and anxiolysis [6]. Flurazepam hydrochloride is a benzodiazepine derivate known as a hypnotic. It has a quick starting time 0.5-1 h and a long half-life and indicated as a hypnotizing agent in different sleep trials [7].

Recently, investigators have found the efficacy of the  $\alpha_2$  (alpha-2-delta) voltage-subordinate calcium channel blockers (gabapentin and pregabalin) for the treatment of preoperative anxiety [8]. Gabapentin is an analgesic tranquilizer that is powerful for neuropathic pain. It specifically hinders the nociceptive receptors by acting at central nervous system. Pregabalin has better pharmacokinetic properties with maximum plasma levels at one hour after oral dosage. This pharmacokinetic profile makes oral pregabalin significantly more effective for preoperative anxiolysis than gabapentin [9].

Subjective feeling of anxiety is common characteristics of the preoperative phase [10]. Though a couple of researchers suggest that mild to severe preoperative anxiety is associated with improved postoperative outcomes in adults [11]. Several researchers reported that a high preoperative anxiety was related to both psychological and physical consequences [12, 13]. A preoperative anxiety has been linked to extended postoperative pain, extended postoperative use of analgesics, and delayed recovery [14]. It has been demonstrated that a high proportion of patients admitted to surgical ward for elective surgery encounter anxiety preoperatively [15]. This review aimed to summarize the pharmacological interventions used to control of preoperative anxiety.

## Methods

An electronic search in MEDLINE and EMBASE was done using a combination of keywords. The search resulted in 73 studies, which were screened for eligibility criteria such as clinical trial design, English language, and human studies. After exclusion of ineligible, duplicated and review studies, the full text of the eligible studies were screened and the data were extracted. The characteristics for which data were collected included sample size, age of patients, type of surgery, medications used to reduce anxiety, dose and regime of medications, effect of reduction in anxiety. The findings of the review summarized in table of inclusion studies.

## Results

The search of the literature, after exclusion of ineligible studies, revealed 14 studies met the inclusion criteria [16-30]. Included studies aimed to investigate, from randomized controlled trials (RCTs), the pharmacological interventions for control of preoperative anxiety. The total number of included patients was 983, of them adult subjects was 556 [16,17,20,21,23,26,28,31] with the age range of 18-70 years and 427 children [19,22,25,29,32] with the

age range of 1-11 years. Some of the included placebo-controlled trial [16,17,20,21,23,26,28-32] while active control were recruited in other studies [19,22,25,32].

Regarding the type of surgery for which preoperative anxiety was assessed, they include reconstructive burn surgery [29], elective laparoscopic gynecologic procedures, plastics, ear nose & throat, minor orthopedic surgery [16], total hip arthroplasty [23], urologic, inguinal herniorrhaphy, hydrocele repair, circumcision, orchidopexy [25], arthroscopic anterior cruciate ligament repair using hamstring autograft [26], ambulatory lower abdominal surgery [27], otolaryngologic surgery [28] and removal of impacted third molars [30] were the different types of surgical procedures included in this review. Four included studies investigated the effect of gabapentine [16,20,26,31] while three studies investigated the effect of pregabalin [17,21,23], four studies evaluated midazolam [19,22,25,32] one study used tandospirine [28], other study used lorazepam [29] and finally one study investigated the effect of flurazepam [30]. Regarding the main outcome which is the reduction of preoperative analgesia reported in many included studies [16,19,21,22,25,26,28,29,31] while no difference appeared in other studies [17,20,23,30,32].

## Discussion

As anxiety increases preoperatively, persistent preoperative personal satisfaction still controversial [33]. A wide range of methodologies, including educational approach [34] and even music [35,36], have been examined to decrease preoperative anxiety, which can increase postoperative pain. Among the mental outcomes of anesthesia and surgery, numerous authors have depicted the event of postoperative behavioral issue. Preoperative administration of anxiolytics in pediatrics appears to be fundamental as an anxious children has 3.5 times more serious hazard to create postoperative behavioral issue [22]. The utilization of midazolam decreases the rate of bad dreams and waking during the evening [37].

preoperative anxiety levels were accounted for to be reduced in patients who received gabapentin 1200 mg [26] and are in agreement with the outcomes by White

and his colleagues regarding pregabalin prescribed for preoperative anxiety [23]. It is well-known that doses lower than 1,200 mg were not associated with plasma levels which expected to create clinical anxiolytic effect [38]. A considerable perioperative trials detailed, the dosage of 1200 mg of gabapentin orally pre-surgery is safe and has just minor side effects [31]. However the safety of gabapentin in elderly with diminished renal function require additional studies. The utilization of gabapentin may be restricted by its already known side effects such as dizziness, drowsiness, weakness, tired feeling, nausea, diarrhea, constipation, and ataxia. Sedation, laziness and unsteadiness that have a tendency to happen at the higher doses of the medication may compromised its anxiolysis [39].

Reducing preoperative anxiety with gabapentin may have additional benefit of controlling postoperative pain and decreased morphine consumption in light of the fact that there is a relationship between preoperative anxiety and postoperative pain [5]. Pregabalin has an indistinguishable pathway from gabapentin and is likewise utilized for treating anxiety issue. A preoperative oral dose of 300 mg pregabalin brought about a similar anxiety score as an oral dosage of diazepam 10 mg. The advanced pharmacokinetic profile of pregabalin makes pregabalin considerably more appropriate for treating preoperative anxiety in adults than gabapentin [16].

## Conclusions

Benzodiazepines remain the medication of choice for the treatment of preoperative anxiety. However, many cautions should be taken in using preoperative medications among specific groups of patients such as hypersensitive reaction or physical dependence on the prescription. A strong correlation regarding benzodiazepines is justified. Additionally more randomized control trials to support use of gabapentin for the treatment of preoperative anxiety.

## Conflict of interests

The authors declared no conflict of interests.

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