# A pill against fear and phobia? The effects of propranolol on memories of individuals suffering from dental phobia. A prospective double blind randomized controlled trial.

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The aim of the study is to examine the effect of propranolol on intrusive memories of people suffering from a specific phobia (i.e. dental phobia). It is hypothesized that the administration of propranolol prior to dental treatment:1. would be...

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|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Pending |
| **Health condition type** | Anxiety disorders and symptoms |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON34861

**Source**
ToetsingOnline

**Brief title**
A pill against fear and phobia?

### Condition

- Anxiety disorders and symptoms

**Synonym**
anxiety

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Universiteit van Amsterdam
**Source(s) of monetary or material Support:** Ministerie van OC&W

## Intervention

**Keyword:** dental anxiety, memory, phobia, propranolol

## Outcome measures

### Primary outcome

- The primary outcome measure used in this trial is the Short version of the Dental Anxiety Inventory (S-DAI; Aartman, 1998). The S-DAI is a nine-item scale measuring dental anxiety. Responses are scored 1*5, giving total scores ranging from 9 (not anxious at all) to 45 (extremely anxious).

- VAS-scales that assess various aspects of the memories. For example, patients will be asked to rate the extent to which various emotions (e.g., sad, guilty, ashamed, anxious, angry, helpless) accompanied their memories, on a scale from 0 (not at all) to 100 (very much so). In addition, patients will be asked to rate the vividness of two key-memories, their sense of *nowness* and re-experiencing of physical sensations and emotions that were present in the original event, impact in terms of interference with daily activities, uncontrollability, and distress caused by the intrusion over the past week.

### Secondary outcome

- To be able to accurately measure PTSD symptom severity on a continuous scale the Dutch version of the Impact of Event Scale-Revised (IES-R; Weiss & Marmar, 1997) will be used. This scale consists of 22 items constituting the subscales intrusions, avoidance and hyper arousal. When scoring the IES-R, subjects are

asked to indicate how frequently the symptoms had been present during the past seven days. The frequency of each symptom is scored using a 5-point (0*4) response format with equal intervals, ranging from *not at all* (0) to *very much* (5). The scores can be summed to produce a total IES-R score (range 0* 110) with a higher score indicating a greater level of post-traumatic stress phenomena.

- The Korte Klachten Lijst (KKL; Lange, Schrieken, van de Ven & Blankers, 2000) will be used to assess level of psychopathological symptoms. The KKL consists of 14 items with a 4-point scale and is a short version of the SCL-R-90 measuring the same dimensions (Arrindell & Ettema, 1986). For the present study, the total score is used. This is the sum of the items, and can vary between 0 and 56. .

# Study description

**Background summary**

If someone suffers from a marked fear that is excessive or unreasonable, cued by the presence or anticipation of a specific object or situation it is likely that this person has a specific phobia (American Psychiatric Association, 2000). Specific phobia is the most prevalent anxiety disorder with a prevalence rate of 10-12% (Bijl, van Zessen & Ravelli, 1997; Oosterink, De Jongh & Hoogstraten, in press). It is also a debilitating condition. A large epidemiological study of over 20,000 people in 6 different countries (ESEMeD-project), showed that having a specific phobia is associated with more sick leave (11% over the past 30 days) than other mental disorders including alcohol addiction (3%), depression (9%) or purely somatic conditions, such as cardiac disease (7%) and diabetes (2%; Alonso et al., 2004).
While some phobias appear to be acquired following a specific traumatic experience with the phobic stimulus, such events are rarely found in the etiology of others. For example, it has been found that the most common category of phobic fears, phobias of harmless animals (e.g. spiders, mice, bats etc.) are not the result of an experience associated with terror or pain

(Davey, 1992). Likewise, a study among water-phobic children showed that only 2% of the phobias could be attributed to a direct conditioning event after which water was subsequently feared (Menzies & Clark, 1995). Conversely, there are particular types of fears which are almost exclusively related to confrontations with a traumatic stressor.

A typical example of a traumatically induced type of specific phobia (i.e., *traumatic phobia*, McNally & Saigh, 1993) is dental phobia. In some studies, 96% of a group of anxious dental patients indicated having experienced one or more terrifying dental treatment events that could explain the onset of their dental fear or phobia (Locker, Liddell, Dempster, & Shapiro, 1999). To this end, the experience of helplessness appears to have the greatest potential risk of precipitating pathological forms of dental anxiety (Oosterink, De Jongh & Aartman, 2009). As individuals tend to construct highly negative images and dysfunctional cognitions of such events (De Jongh & Ter Horst, 1993; De Jongh et al., 1994), phobic individuals, like those suffering from posttraumatic stress disorder (PTSD), are likely to experience excessive retrieval of fearful memories of past horrific events (De Jongh, Aartman & Brand, 2003). Research indicates that such memories are difficult to suppress (De Jongh et al., 1996; Muris et al., 1998), and as phobias are characterized by fear networks of high associative strength, confrontation with a phobic stimulus is likely to provoke retrieval of stimulus-associated fear memories with a strong physiological response (Cuthbert et al., 2003; Foa & Kozak, 1986; Lang, 1985). Research supports this notion showing that images of previous distressing events, and associated negative beliefs, are not only triggered by a direct confrontation with a phobic object or situation, but also in anticipation of such an event, and can even occur spontaneously (De Jongh, Fransen, Oosterink-Wubbe & Aartman, 2006). There are indications that every reactivation of such aversive experiences further strengthens the aversive memory trace (De Quervain & Margraf, 2008). This means that activation of aversive memories not only plays an important role in the symptomatology of fears and phobias, but also in the process contributing to the maintenance, and aggravation of these conditions.

Last century much progress has been made in understanding the process of consolidation and re-consolidation of memories (Cahill & McGaugh, 1998; Lechner et al., 1999). In this process a brain structure termed the amygdala is crucial since it is involved with the formation of enhanced declarative memory for emotionally arousing events (Cahill & McGaugh, 1998; McGaugh, 2000; Phelps, 2004). In a threatening situation adrenaline and noradrenaline (or epinephrine and norepinephrine) are released by the adrenal medulla which mediates the body's short term stress response, leading to vasoconstriction, increased heart rate, a higher blood pressure and sweat production. Adrenaline is also released as a neurotransmitter in the brain. This stress hormone leads to a state of alertness and has been found to modulate the processing of emotional information via the amygdala (van Stegeren, 2008). What is less known is that the endogenous stress hormones feed back directly to the amygdala to strengthen the long term memory of the same events that initially induced their release (Cahill, 2003). As adrenaline seems to enhance memory in a dose-dependent way glucocorticoids have an important adaptive function in response to stressful

experiences. That is, in addition to give rise to an immediate response to an emotional event, these hormones aid future responses by enhancing declarative memory of this event.
A large proportion of people suffer from conditions that result from the personal experience of something terrible and the disturbing effects of how it is remembered. Both PTSD and dental phobia are excellent examples of such conditions. In order to effectively treat the symptomatology it would be necessary to be able to transform the way this experience is encoded. This would require some type of intervention that blocks or diminishes the human stress response as this would help reconsolidating the memory of an emotionally powerful experience into a less emotionally charged form, resulting in less re-experiencing and thus in a reduced fear response. There is evidence to suggest that the ß-adrenergic blocker propranolol is physiologically capable of doing this.

Brunet and his colleagues investigated the effect of the ß-adrenergic receptor antagonist propranolol on the alleviation of PTSD symptoms (Brunet et al., 2008). In this study, 19 individuals with chronic PTSD were asked to describe the event that caused their PTSD, in order to reactivate their traumatic memories. Immediately following this intervention, subjects received either 40 mg of short-acting propranolol and two hours later 60 mg of long-acting propranolol or twice a placebo. A script of this traumatic event was created and after a week subjects had to listen to their personal script again. It was found that when propranolol was provided within hours after their mental imaginary, physiologic responses (i.e. heart rate and skin conductance) two weeks later were significantly smaller in the propranolol than in the placebo group, suggesting a long-lasting effect of propranolol on memory.
Thus, elevated levels of propranolol seem to interrupt the vicious cycle of spontaneous retrieving, re-experiencing and the reconsolidation of negative or traumatic memories and, thereby, promote forgetting (De Quervain & Margraf, 2008). A recent study on the acquisition and alleviation of spider fear supports the notion that a fear response can be weakened by disrupting the reconsolidation process, and that this disruption may prevent the return of fear (Kindt, Soeter & Vervliet, 2009). In their study, 60 undergraduate students aged 18 to 28 viewed fear-related images on a computer and learned to link pictures of spiders with a mild shock to the hand, which created a fearful memory. After a 24-hour break, the researchers randomly gave each participant either 40 milligrams of propranolol or a placebo. An hour and a half later, they asked the students to view the spider pictures again and to remember what they had learned the day before. The students who received propranolol showed no eye blink startle reflex when viewing the spider pictures, a finding that suggests the entire fear memory was removed. The results of this study suggest that propranolol exerts effects on the memory system by disrupting the reconsolidation process. According to the authors the results may be explained by the fact that the beta-adrenergic blockade during reconsolidation selectively disrupts the protein synthesis of the amygdalar fear memory, which may result in *deconsolidation of the fear memory trace while leaving the

declarative memory in the hippocampus untouched* (Kindt, Soeter & Vervliet, 2009. Limitations of this study are that the subjects did not suffer from a relevant clinical (i.e. phobic) condition and that only a behavioral expression of the fear response (i.e., startle reflex) was measured. Furthermore, it is not clear whether the memory effects resulted in a long-term reduction of spider fear.
If memories of spiders are indeed amendable to the effects of propranolol then it could be assumed that people with dental fear could also profit from this intervention. Indications that propranolol potentially has the possibility of inducing positive effects on peoples* phobic fear response come from a study conducted by Liu et al. which showed that administering propranolol at least temporarily reduces dental patients* level of state anxiety during dental treatment (Liu, Milgrom & Fiset, 1991). In this study 23 subjects who met the DSM-III-R criteria for simple phobia received an individual dosage of either propranolol or placebo prior a dental treatment, and performed a behavioural avoidance test consisting of actual dental treatment. Results showed a reduction in self-reported anxiety, pain intensity and aversiveness during the injection phase of dental treatment following propranolol. Although these results are promising, since no follow-up was included, it remains uncertain whether the reduced physiologic responding is permanent and to what extent propranolol has the ability to cause long standing changes in anxiety and related conditions.

**Study objective**

The aim of the study is to examine the effect of propranolol on intrusive memories of people suffering from a specific phobia (i.e. dental phobia). It is hypothesized that the administration of propranolol prior to dental treatment:
1. would be associated with alleviation of patients* level of emotional arousal (i.e., heart rate) and reduction of self-reported anxiety during treatment.
2. would be associated with a reduction of the emotional intensity, aversiveness and intrusiveness of: a.) the key memory associated with person*s dental phobia immediately following treatment, and at four weeks follow-up, and b.) the memory of the dental treatment four weeks following the treatment.
3. would be associated with a reduction of dental trait anxiety at four weeks follow-up.
4. Further, is hypothesized that the administration of propranolol perse (i.e., without memory activation) would not have effect on any of the outcome variables.

**Study design**

Sixty patients with specific phobia according to the structured interview for DSM-IV (First et al., 2002) will be randomly assigned to one of two groups. Patients in both groups will receive their regular dental treatment (i.e. fillings, root canal treatments and/or extractions) to expose them to the

dental situation and reactivate earlier dental memories.
One group will receive propranolol prior to treatment, while the subjects of the other groupwill get a placebo administered.
An independent dentist blinded to group allocation will assess all participants using the scores on a series of standardized outcome measures on entry to the study (at baseline), on completion of dental treatment (post-treatment), and finally at a four weeks follow-up assessment.

**Intervention**

After a standardized period of 14 days after initial assessment all patients we be re-assessed using the same self-report measures as administered at the initial assessment. Patients return for routine dental treatment in the morning of the day of their appointment. Two hours before treatment subjects take either a propranolol or a placebo capsule (40 mg), which will specifically be prepared by the pharmacology department of the Vrije Universiteit.
After a 30 seconds baseline period patients will be requested to listen to the script of the most crucial memory, composed two weeks before, and imagine the event for a 30s-period. Next, patients will be asked to rate the extent to which various emotions accompanies the memory, to rate the vividness of the memory, sense of *nowness* and re-experiencing of physical sensations and emotions which were present in the original event, impact in terms of interference with daily activities, uncontrollability, and distress caused by the intrusion of the memory over the past week. Also heart rate and blood pressure will be recorded. After this, regular dental treatment starts.
Immediately following treatment, data regarding operative psychological distress (i.e., pain, anxiety and emotional disturbance during treatment) will be obtained using three separate visual analogue scales (VASs), ranging from 0 (*not at all painful/anxious/disturbing*) to 100 (*extremely painful/anxious/disturbing*). Also other operative variables that will be examined as potential predictors of increased levels of anxiety and occurrence of trauma-related symptoms.
All patients will be asked to repeat their medication (propranolol 40 mg or placebo pill) two times, with four hours in between.

Follow up assessment
After four weeks when all participants return back for the follow-up appointment no propranolol will be administered. They will be asked to bring up two memories: the initial, most crucial memory related to the dental phobia and the memory of the treatment four week earlier. First, patients are asked to rate the extent to which various emotions accompanied the initial memory, to rate the vividness of this memory, sense of *nowness* and re-experiencing of physical sensations and emotions that were present in the original event, impact in terms of interference with daily activities, uncontrollability, and distress caused by the intrusion over the past week. Next, after a 30 seconds baseline period subjects listen to the script, and imagine the event for a 30s-period during which heart rate and blood pressure are recorded. The same is

repeated but now for the memory of the dental treatment four weeks previously. Next, the dental treatment starts. Immediately following treatment, data regarding operative psychological distress (i.e., VASs on pain, anxiety and emotional disturbance during treatment) as well as data on other operative variables will be obtained.

### Study burden and risks

Many patients request some type of drug for their symptoms of state anxiety, as they find it hard to deal with the dental traetment situation, but until now these have not been found to be safe or have negative effects in term of re-learning. Thus, the participants may profit from this intervention. Propranolol is a widely used and relatively safe product with limited side effectsof which the most important are: fatigue, slow pulse, cold extremities, sleep disturbances and nightmares.

## Contacts

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## Trial sites

### Listed location countries

Netherlands

## Eligibility criteria

### Age

Adults (18-64 years)
Elderly (65 years and older)

### Inclusion criteria

Patients will be admitted to the study if they present with a formal diagnosis of specific phobia (i.e., dental phobia), are over 18 years, and are willing to give informed consent.

### Exclusion criteria

Patients will be excluded if they present with (a) a systolic blood pressure (SBP) <100 mm Hg; (b) asthma, heart failure, heart block, a cardiac arrhythmia, or insulin-requiring diabetes; (c) previous adverse reaction to a ß-blocker; (d) use of another ß-blocker; (e) pregnant or breast feeding; and (f) being in therapy elsewhere if not willing to suspend that treatment until the end of the study.

## Study design

### Design

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|---|---|
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Double blinded (masking used) |
| Control: | Placebo |
| Primary purpose: | Treatment |

### Recruitment

NL

| | |
|---|---|
| Recruitment status: | Pending |
| Start date (anticipated): | 01-04-2010 |
| Enrollment: | 60 |
| Type: | Anticipated |

### Medical products/devices used

| | |
|---|---|
| Product type: | Medicine |

| | |
|---|---|
| Brand name: | propranolol |
| Generic name: | propranolol |
| Registration: | Yes - NL outside intended use |

## Ethics review

Approved WMO

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|---|---|
| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |

## Study registrations

### Followed up by the following (possibly more current) registration

No registrations found.

### Other (possibly less up-to-date) registrations in this register

No registrations found.

### In other registers

| Register | ID |
|---|---|
| EudraCT | EUCTR2010-018229-20-NL |
| CCMO | NL31184.018.10 |