Prevention & Treatment, Volume 6, Article 1, posted June 23, 2003

Open Versus Hidden Medical Treatments: The Patient's Knowledge About a Therapy Affects the Therapy Outcome

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ABSTRACT

Any medical treatment has 2 components, the first being the specific effects of the treatment itself, the second, the knowledge that the treatment is being performed (the placebo effect). So far, the placebo effect has been studied by eliminating the specific effects of the therapy through the administration of a dummy treatment. In this study, the authors reversed this experimental approach. In fact, whereas the specific effects of the treatment were maintained constant, the patient's knowledge that the therapy was being performed was done away with. To do this, the authors performed hidden medical treatments and compared these with the open ones. The results show that the hidden administrations of pharmacological and nonpharmacological therapies are less effective than the open ones.

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This work was supported by grants from the Italian Ministry of University and Research, from the project Neuroscience of the National Research Council (01.00439.ST97 and 02.00529.ST97) and from the project Alzheimer's Disease of the Italian Ministry of Health (PFA/DML/UO6/2001 and PFA/DML/UO6/2001/AA).

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A medical treatment that is carried out in routine medical practice has two components: one related to the treatment itself and the other coming from the knowledge that the therapy is being performed. The latter is better known as the *placebo effect*. So far, the placebo component of a medical treatment has been studied by simulating a therapy through the administration of a dummy medical treatment (the placebo), in order to eliminate the specific effects of the therapy itself. In the present study, we changed this experimental approach completely by eliminating the placebo component and maintaining the specific effects of the treatment.

The placebo effect is a complex phenomenon, and much of it is due to the context around the therapy (Benedetti, 2002; Benedetti & Amanzio, 1997; Di Blasi, Harkness, Ernst, Geirgiou, & Kleijnen, 2001; Guess, Kleinman, Kusek, & Engel, 2002). If the outcome is compared with an untreated (or natural history) group, the real placebo effect can be found (Fields & Levine, 1984). This approach has yielded important results in the validation of new therapies (de Craen, Kaptchuck, Tijssen, & Kleijnen, 1999; Guess et al., 2002; Kaptchuck, 1998)—for example, antidepressant medications (Kirsch, Moore, Scoboria, & Nicholls, 2002; Kirsch & Sapirstein, 1998)—as well as in the understanding of the biological mechanisms underlying the placebo effect (Amanzio & Benedetti, 1999; Benedetti, Arduino, & Amanzio, 1999; de la Fuente-Fernandez et al., 2001; Levine, Gordon, & Fields, 1978; Mayberg et al., 2002; Petrovic, Kalso, Petersson, & Ingvar, 2002).

A few attempts have been made to eliminate the patient's awareness that a therapy is being received (Amanzio, Pollo, Maggi, & Benedetti, 2001; Levine & Gordon, 1984; Levine, Gordon, Smith, & Fields, 1981) or, otherwise, that an experimental study is being carried out (Bergmann et al., 1994; Dahan et al., 1986). For example, if an intravenous analgesic injection is performed covertly, analgesia will be less effective compared with an open injection in full view of the patient, indicating that the effectiveness of a painkilling treatment depends in part on the subject's knowledge that a therapy is being performed (Amanzio et al., 2001). The difference between open and hidden injections has been considered to represent the placebo effect, or at least its major component resulting from the patient's perception of the administration of the agent (Amanzio et al., 2001; Price, 2001). Thus this placebo component can be assessed without placebo groups. On the basis of these considerations, we studied the effects of eliminating the patient's knowledge that a therapy is being administered. To do this, we compared open and hidden medical treatments in five different conditions.

Method

The Informed Consent

In a previous study (Amanzio et al., 2001), we performed hidden administrations of different painkillers in both the clinical and the laboratory setting. In the latter, healthy volunteers were told that they could receive either an active drug or a placebo or nothing, thus giving their informed consent to receiving different treatments. Therefore, when a hidden infusion of a painkiller was performed, these subjects believed that nothing was being administered. In the clinical setting, the situation was quite different but suitable for hidden manipulations, which, we believe, were ethically correct for at least two reasons. First, the patients knew that they could receive either an analgesic treatment or nothing, depending on many factors, such as their pain intensity, ventilation, and the like. Second, they received the usual postoperative analgesic therapy, without any modification with respect to the routine procedures. The only difference was a doctor-initiated versus a machine-initiated treatment.

Accordingly, in the present study we selected three clinical conditions in which drugs and medical treatments are not necessarily started or stopped with the patient's awareness, as explained in more detail below.

1. Our postoperative patients were told that they could receive either a painkiller or nothing, depending on their clinical condition (respiratory function, urinary function, and such), and that they were not necessarily informed when the analgesic treatment was started. In this way, they did not know *if* and *when* the treatment was given. This is exactly what happens sometimes in routine clinical practice-that is, patients accept to receive a painkiller but they do not know when the infusion machine starts delivering the medication.
2. The same approach is true for the antianxiety treatment.
3. As to the Parkinsonian patients, they usually come to our department every month, and different manipulations of the subthalamic stimulus intensity are performed in order to check and adjust the stimulation parameters. The type of manipulation (either increase or decrease of the stimulus) is not necessarily specified to the patient, as described in a recent study of our group (Pollo et al., 2002). Therefore, this is a good situation in which open and hidden reductions of the stimulus intensity can be studied. In this case also, we believe that it is ethically correct to manipulate the stimulus intensity after the patients have given their informed consent, even though they do not know if and when the stimulus is increased, decreased, or turned off.

As far as the healthy volunteers are concerned, they were told that either an active drug (b-blocker or muscarinic antagonist) or nothing could be administered. Therefore, although they gave their informed consent, they did not know if and when the drug was administered. All the subjects were randomly assigned to either the open or the hidden treatment. All the protocols were consistent with the principles of the Declaration of Helsinki (World Medical Association Declaration of Helsinki, 1997), particularly in the clinical setting, where all patients, in both the open and hidden groups, received the standard of care.

Postoperative Pain

A total of 42 patients (Table 1) were studied with open and hidden administrations of morphine in the postoperative phase, according to the procedures used in our previous study (Amanzio et al., 2001). Briefly, the patients underwent thoracotomy with the resection of at least three of the following muscles: latissimus dorsi, serratus anterior, trapezius, and rhomboid. Anesthesia was induced with fentanyl, 150-250 g iv, and maintained with isoflurane and oxygen. Paralysis was achieved by means of atracurium (30-50 mg) and reversed with 1 mg atropine and 2 mg neostigmine (iv). One hour after recovery from anesthesia, a 0.14 mg/kg dose of morphine sulfate was given through an intravenous line by means of an infusion pump. The infusion rate was 0.014 mg/kg/min, for a total infusion time of 10 min. Whereas 21 patients received an open infusion from a doctor, the remaining 21 received a hidden infusion from a preprogrammed infusion machine. The open administration was performed at the bedside by a doctor, who told the patients that the medication was a potent painkiller, according to routine clinical practice. In other words, the patients were informed that their pain was going to subside within a few minutes. By contrast, the hidden administration was given by the preprogrammed machine without any doctor or nurse in the room, so that the patients were totally unaware that a painkilling medication was being given. Thus, the main difference between open and hidden injections was the knowledge that a medication was being given. Both the open and the hidden groups rated their pain by themselves on a diary at 30 and 60 min after morphine infusion, on the basis of a numerical rating scale ranging from 0 = *no pain* to 10 = *unbearable pain*.

Table 1
Subject Characteristics—Postoperative Pain

	Open administration of morphine	Hidden administration of morphine	Open interruption of morphine	Hidden interruption of morphine
Sex (male/female)	11/10	13/8	9/9	9/9
Age (years)	56.5±9.5	53.9±11.8	55.6±8.4	54.1±9.7
Weight (kg)	65.4±9.1	63.6±10.1	62.5±8.7	63.9±11.3

Another 36 thoracotomized patients (Table 1), after having received morphine for 48 hr (20 mg/24 hr), underwent either an open (n = 18) or a hidden interruption (n = 18) of the morphine. In the open condition, the patients were told that morphine had been stopped and that they had to fill in a pain diary and, if needed, could request a painkiller. In the hidden condition, morphine was stopped without telling the patient anything. They were told only that painkillers were available if necessary and on request.

State Anxiety

Another 30 thoracotomized patients (Table 2), with the same characteristics as those described above,

were studied with open (n = 15) and hidden (n = 15) administrations of diazepam in the postoperative phase. These patients showed above normal state anxiety, as assessed by means of the State–Trait Anxiety Inventory—State Version (STAI–S; Spielberg, Gorsuch, & Luschenne, 1980). They were given a 0.14 mg/kg dose of diazepam intravenously, with an infusion rate of 0.014 mg/kg/min and a total infusion time of 10 min. The open and hidden administrations were given with the same procedures as those described for postoperative pain. The STAI–S form was filled in by the patients after 2 hr without any contact with doctors or nurses.

Table 2
Subject Characteristics—State Anxiety

	Open administration of diazepam	Hidden administration of diazepam	Open interruption of diazepam	Hidden interruption of diazepam
Sex (male/female)	7/8	7/8	8/8	9/7
Age (years)	52.7±9.1	53.1±10.6	54.6±10.4	53.9±11.7
Weight (kg)	62.5+10.5	64.4+11.7	61.5+10.2	63.7+10.8
Trait anxiety (STAI–T)	44.3+12.1	42.7+11.8	41.1+11	42+10.9

Another 32 patients (Table 2) underwent either an open (n = 16) or a hidden interruption (n = 16) of diazepam. After diazepam administration for 48 hr (20 mg/24 hr), the infusion was stopped either overtly or covertly, according to the procedures described for postoperative pain. Patients had to fill in the STAI–S every 4 hr.

In order to rule out differences in trait anxiety, these patients were tested for trait anxiety before surgery by means of the State–Trait Anxiety Inventory—Trait Version (STAI–T; Spielberg, Gorsuch, & Luschenne, 1980; Table 2). In the Italian population, the normal STAI–S range is 45.2 ± 12.37 for adult women and 40.17 ± 10.01 for men, whereas the STAI–T normal range is 46.1 ± 11.53 for women and 39.53 ± 9.25 for men (Nattero et al., 1989; Spielberg, Gorsuch, & Luschenne, 1980).

Parkinson's Disease

A total of 10 Parkinsonian patients (Table 3) were studied with open and hidden stimulations of the subthalamic nucleus. They were diagnosed with idiopathic Parkinson's disease, and clinical evaluation was performed by means of the Unified Parkinson's Disease Rating Scale (UPDRS; Fahn, Elton, & Members of the UPDRS Development Committee, 1987). Two electrodes were implanted in the subthalamic nuclei according to the usual neurosurgical procedures (Benazzouz & Hallett, 2000; Hutchinson et al., 1998; Limousin et al., 1998; Lopiano et al., 2001; Rizzone et al., 2001).

Table 3

Subject Characteristics—Parkinson's Disease

Patient	Age (years)	Sex	History of Parkinson's disease (years)	Time from surgery (months)	Stage of disease before/after surgery
1	51	Female	25	19	4.5/3
2	69	Male	15	14	4/2
3	57	Female	13	20	4/2
4	70	Female	19	27	4/2.5
5	62	Male	12	7	3.0/5
6	46	Female	9	5	2.5/2
7	61	Male	12	20	4.0/5
8	67	Male	10	18	3/1.5
9	57	Male	8	9	4/3
10	68	Male	19	9	4.5/2.5

In the present study, we measured the velocity of hand movement by using a movement analyzer, as previously described (Pollo et al., 2002; Zappia, Montesanti, Colao, & Quattrone, 1994). Briefly, the patients performed a visual directional-choice task in which the right index finger was positioned on a central sensor and moved toward a target when a light was turned on. In each test, 15 consecutive movement time trials were carried out, their average representing the final value for that test. Each patient was tested twice, overtly and covertly, in two different days, and the order was randomly changed. In the open condition, the subthalamic stimulus intensity was overtly reduced to 20% of the optimal stimulation, and the patient was told that motor performance was going to worsen. After 2 hr of the routine adjustment of the stimulation parameters, we overtly increased the stimulus intensity from 40% to 100% and told the patients that motor performance was going to return to normal. By contrast, in the hidden condition, the stimulus reduction to 20% and the stimulus increase from 40% to 100% were performed covertly, with the patients completely unaware that such changes were being performed. To do this, the stimulating apparatus was out of the patients' view, so that they did not realize that any manipulation was being performed. In addition, the intensity was changed with small steps of 0.1 volts, in order to avoid tactile and tingling sensations.

β-Blockade in Healthy Volunteers

We studied 24 healthy volunteers (Table 4) in order to assess the effects of open (n = 12) versus hidden (n = 12) administrations of the β-blocker propranolol. The subjects lay down on a bed, and after the insertion of a needle in a vein of the forearm for continuous infusion of NaCl 0.9%, their electrocardiogram (ECG) was continuously recorded by using conventional techniques. Heart rate was analyzed by measuring the beat-to-beat (R-R) intervals of the ECG and then transforming them into frequency (1/R-R). Heart rate

baseline was represented by the mean of 10 R-R intervals just before the injection of propranolol. The response following propranolol administration was analyzed for 15 min. The ECG beat-to-beat series (R-R intervals) were checked for ectopic beats. All these subjects did not show any ectopic beat.

Table 4
Subject Characteristics—Healthy Volunteers

	Open administration of propanolol	Hidden administration of propanolol	Open administration of atropine	Hidden administration of atropine
Sex (male/female)	6/6	6/6	7/6	6/7
Age (years)	29.7±10.1	28.4±10.2	30.1±9.8	28.8±11.1
Weight (kg)	57.5±10.2	56.9±10.3	58.4±11.2	58.2±10.7

The open injection was performed in full view of the subjects, who were told that their heart rate and blood pressure were going to decrease. Propranolol was infused at a dose of 0.2 mg/kg and at a rate of 0.1 mg/kg/min, for a total infusion time of 2 min. By contrast, the hidden injection was performed by a preprogrammed infusion pump, with neither doctors nor nurses in the room and with the subjects completely unaware that any drug was being administered.

Muscarinic Antagonism in Healthy Volunteers

We also studied 26 healthy volunteers (Table 4) in order to assess the effects of open (n = 13) versus hidden (n = 13) administrations of the acetylcholine muscarinic antagonist atropine. The ECG was recorded and analyzed as described above. The open injection was performed in full view of the subjects, who were told that their heart rate was going to increase. Atropine sulfate was infused at a dose of 0.02 mg/kg and at a rate of 0.01 mg/kg/min, for a total infusion time of 2 min. The hidden injection was performed as described for propranolol.

Statistical Analysis

Statistical analysis was performed by means of the t test for the data of postoperative pain, anxiety, propranolol, and atropine, whereas t test for repeated measures was carried out in the Parkinsonian patients. In addition, chi-square was performed for the data of the additional painkillers in postoperative pain. Data are shown as mean ± standard deviation. The level of significance is $p < .05$.

Results

Postoperative Pain

Figure 1A shows that the pain baseline was the same in the two groups, $t(40) = 0.645$, $p = .523$. After the injection of morphine, the pain decrease in the open condition was larger than in the hidden condition at both 30 min, $t(40) = -3.322$, $p = .002$, and 60 min, $t(40) = -4.766$, $p = .001$. Thus, the hidden administration of morphine was less effective than the open one. As to the interruption of morphine, Figure 1B shows that the pain intensity did not differ between the two groups at the time of the interruption, $t(34) = -1.116$, $p = .272$. After the interruption of morphine, the pain increase was larger in the open than in the hidden condition at 2, 4, and 6 hr, $t(34) = 4.712$, $p = .001$; $t(34) = 4.895$, $p = .001$; and $t(34) = 3.351$, $p = .002$, respectively (see Table 5 for additional data). After 6 hr from morphine interruption, some patients started requesting further analgesics. At 10 hr from morphine interruption, 14 patients of the open group and only 6 patients of the hidden group had requested further painkillers, $\chi^2(1, N = 36) = 5.512$, $p = .019$. Therefore, the hidden interruption of morphine prolonged the postinterruption analgesia.

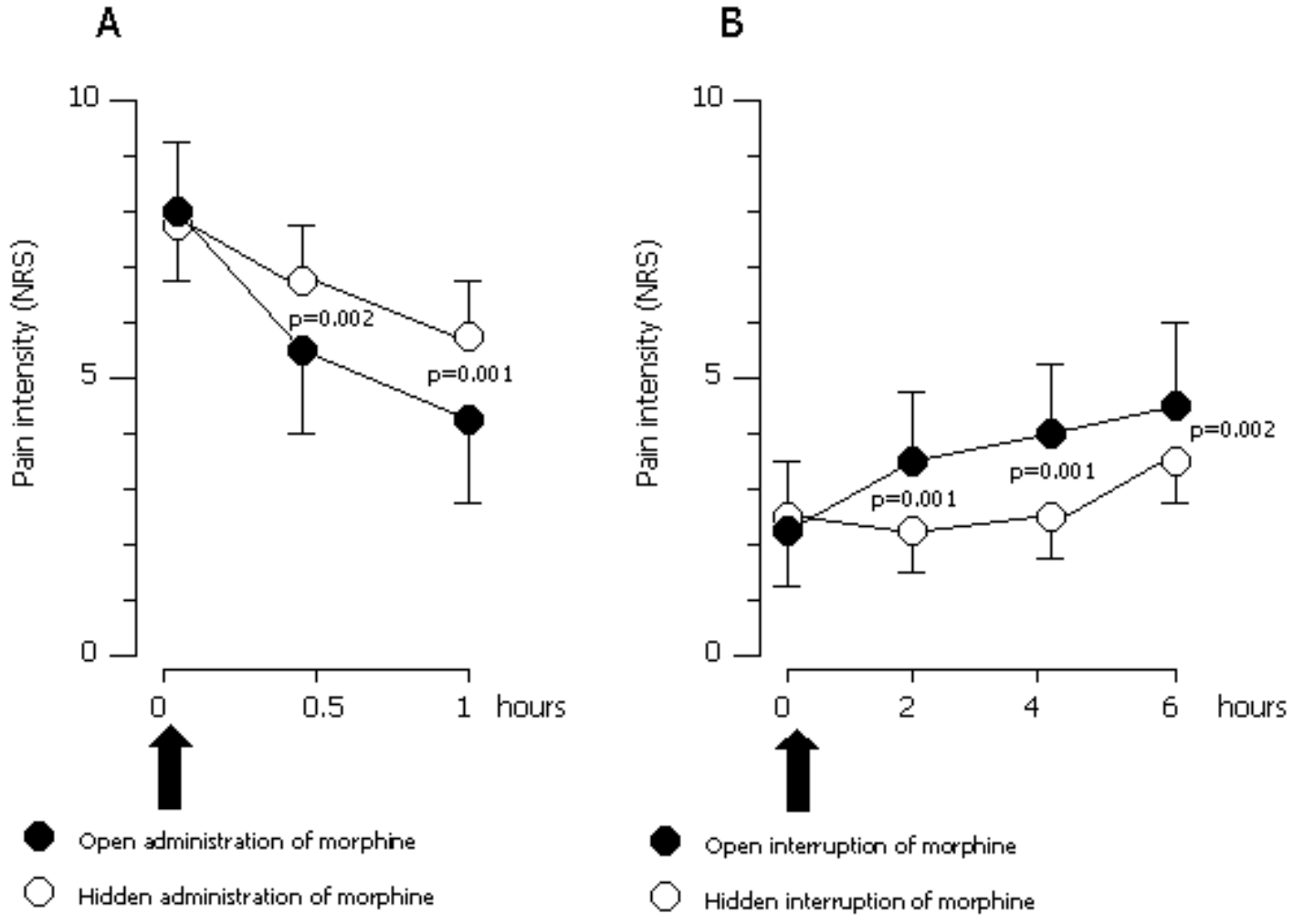

Figure 1. Comparison between open and hidden administrations (A) and interruptions (B) of morphine in postoperative pain. NRS = numerical rating scale.

Table 5

Outcome Measures in the Different Conditions and Their Statistical Analysis

	Outcome of open procedure (*M*±*SD*)	Outcome of hidden procedure (*M*±*SD*)	*t* (*df*)	*p*
Morphine administration (N = 42)				
Pain intensity				
Baseline	7.9±1.1	0.7±0.9	0.645(40)	.523
After 30 min	5.5±1.5	6.7±0.7	–3.322(40)	.002
After 60 min	4.3±1.2	5.8±0.8	–4.766(40)	.001
Morphine interruption (N = 36)				
Pain intensity				
Baseline	2.2±0.9	2.5±0.7	–1.116(34)	.272
After 2 hr	3.5±1.1	2.2±0.4	4.712(34)	.001
After 4 hr	4.1±1.2	2.6±0.5	4.895(34)	.001
After 6 hr	4.5±1.3	3.4±0.5	3.351(34)	.002
Diazepam administration (N = 30)				
STAI–S				
Baseline	49.7±11.3	51.0±11.9	0.307(28)	.761
After 2 hr	37.7±9.5	53.1±10.6	–4.294(28)	.001
Diazepam interruption (N = 32)				
STAI–S				
Baseline	42.4±9.1	40.2±11.2	0.606(30)	.549
After 4 hr	48.5±10.5	40.7±10	2.127(30)	.042
After 8 hr	51.8±12.5	0.6±10.4	3.010(30)	.005
Subthalamic stimulation (N = 10)				
Mov. velocity: m/s				
Baseline	0.30±0.07	0.29±0.07	0.546(9)	.546
After 10 min	0.44±0.1	0.33±0.1	2.577(9)	.030
Subthalamic interruption (N = 10)				
Mov. velocity: m/s				
Baseline	0.45±0.08	0.44±0.09	0.192(9)	.852
After 30 min	0.12±0.06	0.24±0.1	–3.32(9)	.009

Propanolol administration (N = 24)				
	Heart rate: beats/second			
Baseline	72.5±7.4	73.9±8.4	–0.433(22)	.669
After 15 min	62.1±8.9	68.9±7.1	–2.069(22)	.050

Atropine administration (N = 26)				
	Heart rate: beats/second			
Baseline	69.3±8.1	71.6±8.8	–0.693(24)	.495
After 15 min	86.7±10.1	78.5±8.7	2.218(24)	.036

State Anxiety

In Figure 2A it is possible to see the difference between an open and a hidden administration of diazepam. The baseline of the STAI–S was the same in the two groups, $t(28) = 0.307$, $p = .761$, whereas a clear-cut difference was present 2 hr after diazepam administration. In fact, in the open group the STAI–S decreased whereas it did not in the hidden group, $t(28) = -4.294$, $p = .001$. Therefore, diazepam was totally ineffective when administered covertly. As far as diazepam interruption is concerned, Figure 2B shows that at the time diazepam was stopped, the STAI–S was the same in the two groups, $t(30) = 0.606$, $p = .549$. In the open condition, the STAI–S increased after 4 and 8 hr, whereas in the hidden condition it did not change, $t(30) = 2.127$, $p = .042$, at 4 hr and $t(30) = 3.01$, $p = .005$, at 8 hr (see Table 5 for additional data). Thus, the hidden interruption of diazepam did not produce any effect.

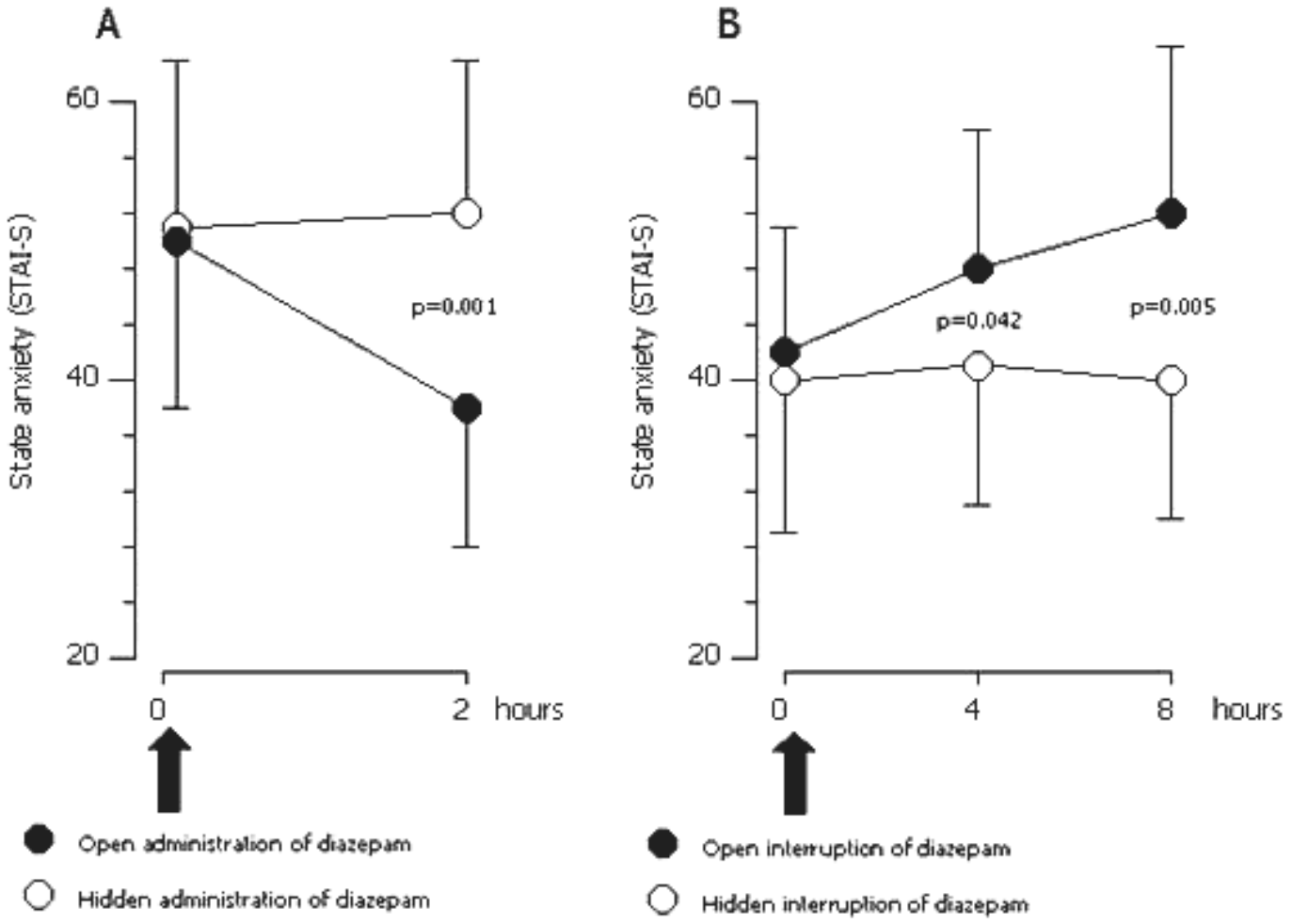

Figure 2. Comparison between open and hidden administrations (A) and interruptions (B) of diazepam in postoperative state anxiety. STAI–S = State–Trait Anxiety Inventory—State Version.

Parkinson's Disease

The open interruption of subthalamic stimulation induced a reduction of movement velocity at 30 min, which was larger than the hidden interruption, $t(9) = -3.32$, $p = .009$, as shown in Figure 3A. Note that no difference in baseline velocity was present between the open and the hidden groups, $t(9) = 0.192$, $p = .852$. Likewise, when the stimulation was increased from 40% of optimal stimulation to optimal stimulation, the open procedure was more effective than the hidden one at 10 min, $t(9) = 2.577$, $p = .03$ (Figure 3B). In this case also, the baseline at 40% of optimal stimulation was the same in the open and hidden groups, $t(9) = 0.546$, $p = .546$. Additional data can be found in Table 5. Therefore, the hidden interruption induced a lesser worsening of motor performance at 30 min, whereas the hidden stimulus increase produced smaller therapeutic effects at 10 min.

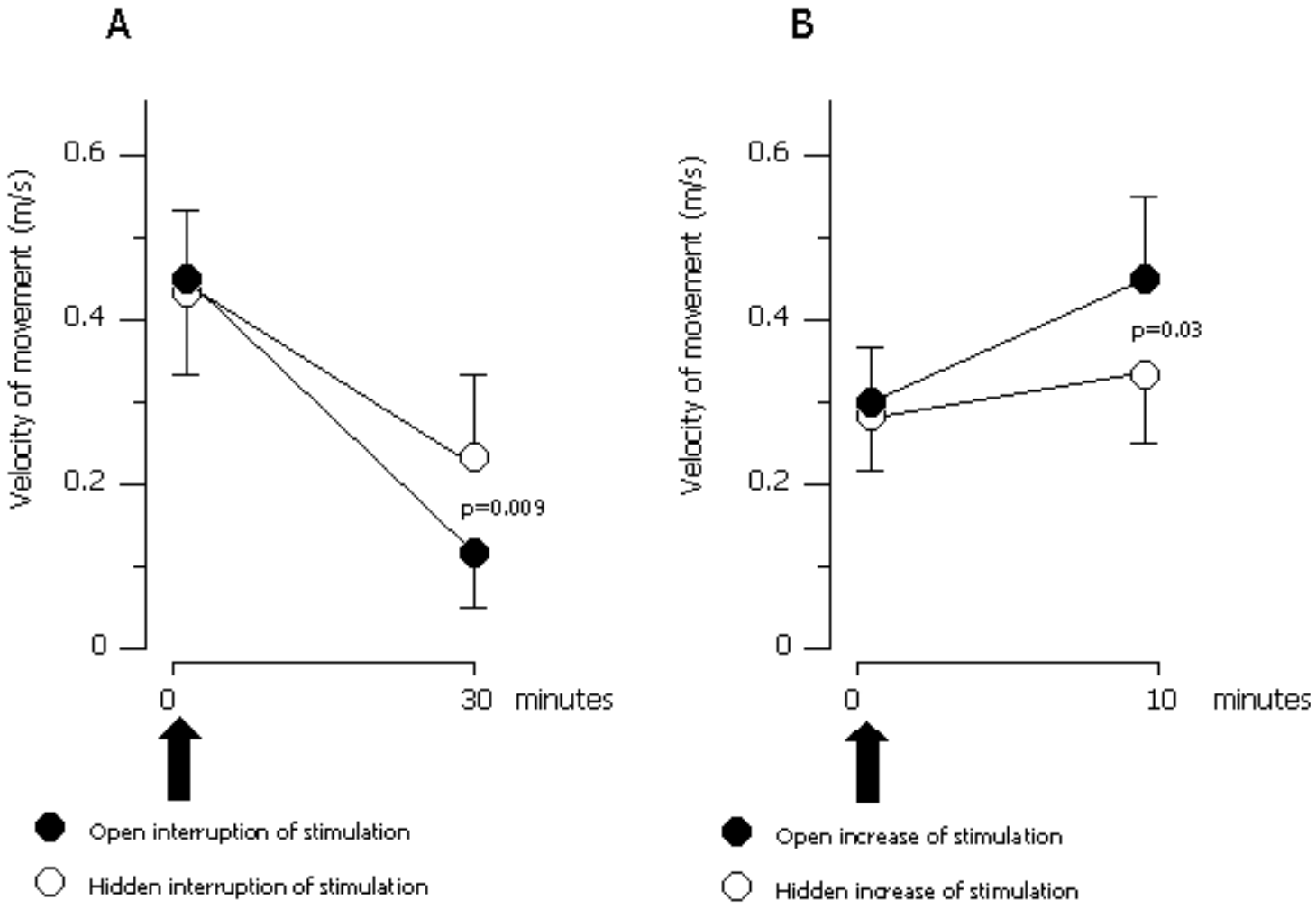

Figure 3. Comparison between open and hidden interruptions (A) and increases (B) of subthalamic stimulation in Parkinsonian patients.

β-*blockade*

The open and hidden groups did not differ in their heart rate baseline, $t(22) = -0.433$, $p = .669$ (Figure 4A). Propranolol was more effective in reducing heart rate when given overtly compared with a hidden administration. In fact, at 15 min after the injection, heart rate was significantly lower in the open condition than in the hidden one, $t(22) = -2.069$, $p = .05$. See Table 5 for additional data.

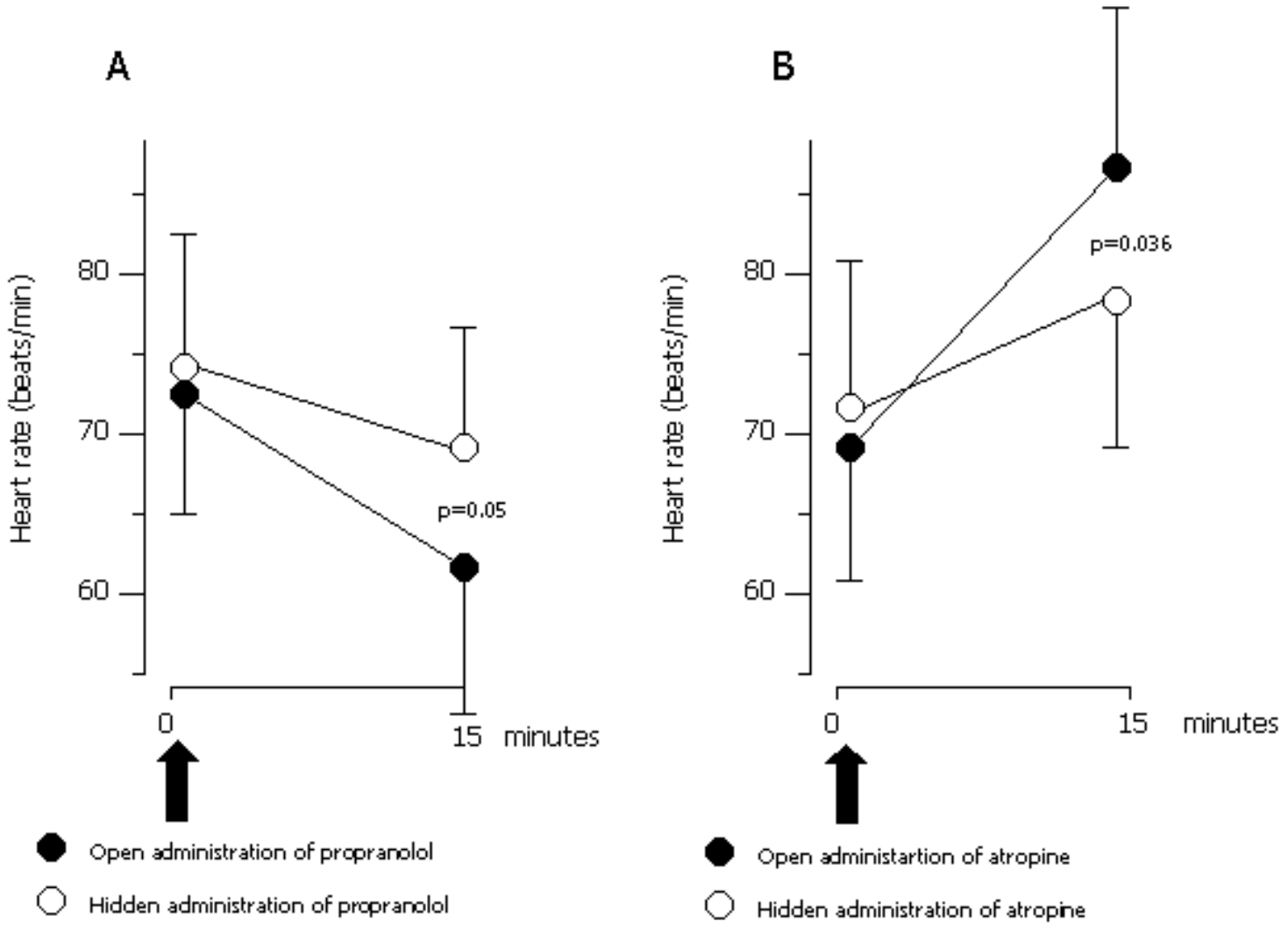

Figure 4. Comparison between open and hidden administrations of propranolol (A) and atropine (B) in healthy volunteers.

Muscarinic Antagonism

In this case also, the open and the hidden groups did not differ in their heart rate baseline, $t(24) = -0.693$, $p = .495$ (Figure 4B). Open atropine produced a larger increase in heart rate than a hidden administration. In fact, at 15 min after the injection, heart rate was significantly higher in the open condition compared with the hidden one, $t(24) = 2.218$, $p = .036$. Additional data can be found in Table 5.

Discussion

The present study demonstrates that the treatments here analyzed are more effective only if the patients know that they are being carried out, thus being in agreement with previous findings on hidden analgesic injections (Amanzio et al., 2001; Levine & Gordon, 1984; Levine et al., 1981) and on hidden participations in experimental studies (Bergmann et al., 1994; Dahan et al., 1986). In our conditions, an open treatment was represented by the administration or interruption of a therapy in full view of the

patient and by informing him or her what was going on, according to what should be the routine clinical practice. Thus, in this situation the patient knew the details of the therapy, why it was being carried out, and what outcomes to expect. By contrast, a hidden medical treatment was represented by the administration or interruption of a therapy with the patient completely unaware that the therapy was being given or interrupted. In this covert situation, no doctors or nurses were in the room, and the treatment was started by a preprogrammed machine. Thus, the main difference between open and hidden treatments lay in the knowledge that the medical procedure was being carried out. In fact, the same drugs, the same doses, the same infusion rates, and the same stimulation parameters were given in both open and hidden conditions. Also, the method of measurement was the same in the two conditions.

However, one of the limitations of the present study is represented by the presence of several confounding variables in the open condition. In fact, in the open administrations we have at least three variables: the awareness of the treatment, the presence of the therapist, and the expectation of the outcome. Therefore, the present study cannot identify which of these factors was the most important. In addition, it is worth remembering the large Pavlovian conditioning literature that has examined the effects of signaled versus unsignaled morphine administration on analgesia in animal models (e.g., Kim, Siegel, & Patenall, 1999; Siegel & Ramos, 2002). These authors found that among rats, signaled morphine administration yields smaller effects than unsignaled administration, an effect that is opposite that observed in the present study. This difference could be explained by the more important role of expectancies in humans compared with animals. Another potential limitation is represented by the involvement of response biases in the open conditions. However, it should be pointed out that whereas these could play a role in the subjective outcomes, like pain and anxiety, they are less plausible for objective measurements, such as motor performance and heart rate changes. It should also be pointed out that although we studied only 10 Parkinsonian patients, the findings on motor performance are in accordance with the other data.

By taking these considerations into account, the open versus hidden treatments represent an interesting approach to better understand the complex psychological factors that are present in any therapy, such as the patient-provider interaction and the awareness of being treated. In particular, the reduced therapeutic effect after a hidden therapy shows that the patient's knowledge about the treatment and/or the doctor-patient relationship are of crucial importance. In the first case, the perception of receiving a treatment induces expectations of therapeutic benefit and hence the activation of a complex cascade of events, such as the release of endogenous opioids (Amanzio & Benedetti, 1999; Benedetti, 2002; Benedetti & Amanzio, 1997; Benedetti et al., 1999; Fields & Levine, 1984; Levine et al., 1978; Petrovic et al., 2002) and dopamine (de la Fuente-Fernandez et al., 2001; de la Fuente-Fernandez, Schulzer, & Stoessl, 2002; de la Fuente-Fernandez & Stoessl, 2002). In the second case, the close interaction of the health care provider with his or her patient is likely to enhance the perception of the treatment that is being performed. Therefore, a close interaction between the doctor and his or her patient can contribute to increase those endogenous mechanisms that are triggered by expectations. For example, it has been shown that the open administration of a painkiller activates the endogenous opioid systems, which in turn potentiate the effects of the painkiller itself (Amanzio et al., 2001).

There are some similarities between the present study and previous investigations that used the so-called balanced placebo design (Knight, Barbaree, & Boland, 1986; Rohsenow & Marlatt, 1981; Sayette, Breslin, Wilson, & Rosenblum, 1994). With this design, some subjects are told that they are getting an

active drug when in fact they are getting a placebo, whereas some other subjects are told they are getting a placebo when in fact they are getting the active drug. These verbal instructions are capable of influencing the effects of both drugs and placebos, thus representing another example of how the knowledge about a therapy affects the therapy outcome.

Although doctors should strive to enhance the patient's knowledge about a therapy, from the present findings it is interesting to note that this is advantageous only when the therapy is being administered. By contrast, if the therapy has to be interrupted, such awareness might be deleterious for the patient. In fact, the open interruption of morphine, diazepam, and subthalamic stimulation produced a greater worsening of the symptoms compared with a hidden interruption. Therefore, if the patient is told that a treatment is going to be stopped, a sort of *nocebo* phenomenon may occur (Barsky, Saintfort, Rogers, & Borus, 2002; Benedetti & Amanzio, 1997). In other words, the expectation of worsening may counteract the beneficial effects that are present after the treatment interruption.

This approach shows that the placebo effect, or at least its major component deriving from the perception that a therapeutic agent is being administered, can be studied without placebo groups (Amanzio et al., 2001; Price, 2001). It is worth emphasizing that the concept of placebo is a complex issue that is difficult to define satisfactorily (Hrobjartsson, 2002). It is probably wrong to call placebo effect the difference between open and hidden treatments, since no placebos are given. Meaning response is perhaps more appropriate (Moerman, 2002; Moerman & Jonas, 2002), in order to make it clear that the crucial factor is not so much the inert treatment per se but rather the meaning around the medical treatment. In other words, placebo effects also occur without the administration of any placebo. Therefore, it might be time to limit the use of the term placebo effect to those situations in which inert (dummy) medical treatments are given (Hrobjartsson, 2002; Moerman, 2002; Moerman & Jonas, 2002). However, it is worth noting that even if a placebo is given, there is no such thing as a *placebo effect*, since this term deflects our gaze from what is really important (the meaning and the meaning-induced expectations) and aims it at what is not (the inert pills and, in general, the inert medical treatments).

The present findings have both clinical and methodological implications. In the first case, every effort should be made to inform the patient what is going on and what should be expected, although a difficult ethical question arises. In fact, whereas this is certainly true when a therapy is started, what about its interruption? In the second case, the open-hidden approach might be a valid complement to the classic placebo-controlled studies, at least in certain circumstances. In any case, the understanding of the differences between open and hidden therapies may help clarify the intricate mechanisms underlying the psychological variables that are present in any medical treatment.

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