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Pharmacology Lecture Series

LECTURE 4

Nocebo effects: Preventing Unintended and Harmful Side Effects

Nov 14, 2017 SON, Room:307

No conflicts of interest to be declared

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Learning objectives

This lecture provides a systematic presentation on framing effects, informed consents and nocebo effects

Objectives:

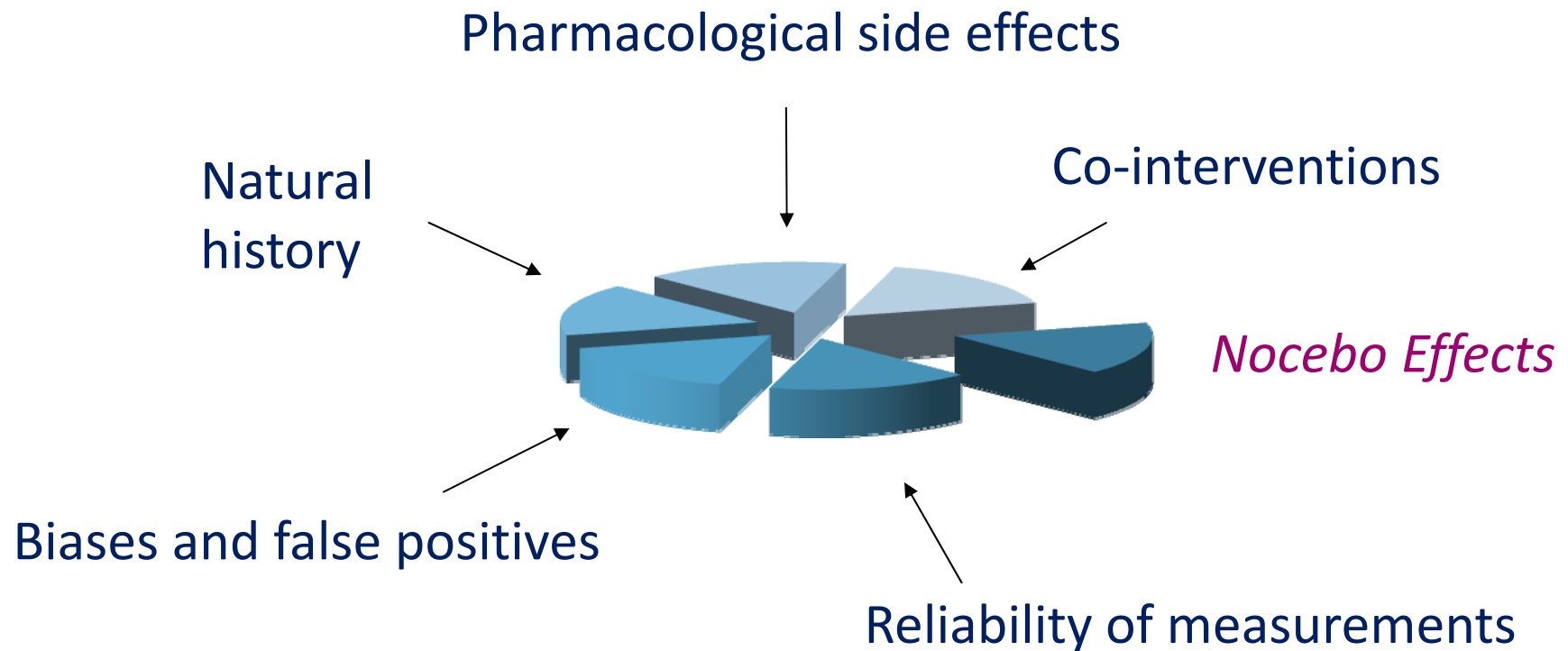
1. Examine the factors that produce clinically-relevant nocebo effects
2. Recommend communication strategies to reduce the occurrence of nocebo effects.



Definitions

- **Nocebo “I shall nocere”:** Term specifically coined to denote the negative counterpart of the placebo phenomenon
- **Nocebo effects:** Neurobiological phenomena wherein patients experienced a symptom worsening

Nocebo effects are not...



EXPECTANCY



Nocebo effects



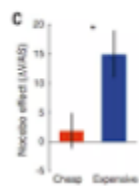
Potent **Nocebo**: The more expensive a harmless cream, the more ...

Ars Technica - Oct 9, 2017

In a new study exploring this mysterious “**nocebo** effect,” researchers ... Center Hamburg-Eppendorf, published the results recently in **Science**.

Side effects are WORSE if you think the drug looks expensive

In-Depth - Daily Mail - Oct 9, 2017



Introducing the “**Nocebo** Effect” and Its Relationship to Packaging

Healthcare Packaging - Oct 11, 2017

A recent Vox article tells of the placebo effect's evil twin, the **nocebo** effect, ... In the study, published in **Science**, the same placebo was used in ...



Pricier meds mean worse side effects, thanks to 'nocebo' effect

Science Magazine - Oct 5, 2017

Then the **scientists** affixed a small device to the volunteers' arms ... lot of research on placebo and relatively little on **nocebo**,” Tinnermann says.

The '**Nocebo**' Effect Triggers Pain That Isn't Actually There

Inverse - Oct 6, 2017



People may expect more side effects from pricier drugs

Chemical & Engineering News - Oct 15, 2017

Scientists don't know as much about this less pleasant effect, ... show that more expensive drugs have stronger **nocebo** effects (**Science** 2017, ...



The **Nocebo** Effect Shows Pain Isn't All in Your Brain

Seeker - Oct 11, 2017

Research into the so-called **nocebo** effect sheds light on the complicated ... In a paper published in the journal **Science**, lead investigator ...

Interactions between brain and spinal cord mediate value effects in placebo hyperalgesia

A. Tinnermann,^{1*} S. Geuter,^{1,2} C. Sprenger,^{1,3} J. Finsterbusch,¹ C. Büchel¹

Value information about a drug, such as the price tag, can strongly affect its therapeutic effect. We discovered that value information influences adverse treatment outcomes in humans even in the absence of an active substance. Labeling an inert treatment as expensive medication led to stronger placebo hyperalgesia than labeling it as cheap medication. This effect was mediated by neural interactions between cortex, brainstem, and spinal cord. In particular, activity in the prefrontal cortex mediated the effect of value on placebo hyperalgesia. Value furthermore modulated coupling between prefrontal areas, brainstem, and spinal cord, which might represent a flexible mechanism through which higher-cognitive representations, such as value, can modulate early pain processing.

Patients in randomized placebo controlled clinical trials frequently discontinue their participation because of side effects. Yet, after unblinding, it turns out that some of these patients were part of the placebo group and thus never received any active medication (1). This is a case of the adverse placebo effect (2, 3) that can be seen in contrast to the

placebo effect. The placebo effect with respect to pain involves an opioidergic mechanism (4–7) and recruits the descending pain modulatory system (5), which targets the spinal cord dorsal horn (8). Placebo effects can be manipulated by providing value information (e.g., price) about a treatment (9–11). Although higher-priced treatments lead to higher placebo effects (11), they might also lead to an increase in perceived side effects. We thus investigated whether value information about a medical treatment can further modulate behavioral placebo effects and the underlying neural network dynamics.

How can a medial prefrontal value signal (10, 12) interfere with central pain processing

and modulate expectation-induced pain perception? One possibility is that this modulation is mediated through functional interactions between key structures of the descending pain pathway (fig. S8) (13). Because placebo hyperalgesia also modulates activity at the spinal level (14), we followed this lead and investigated whether placebo hyperalgesia is mediated through interactions within a cortico-subcortico-spinal network (15), in analogy to other forms of cognitive pain modulation (16, 17). However, simultaneous functional magnetic resonance imaging (fMRI) measurements of neural activity in the brain and spinal cord are technically challenging (18). To investigate the dynamics from cortex to spinal cord, we developed an fMRI method (19, 20) that allows the measurement of neural activity in the entire central pain system, comprising the cortex, brainstem, and spinal cord (figs. S2 and S3).

To study the influence of value on placebo hyperalgesia, we induced negative treatment expectations and experiences in two groups of participants (21). As the placebo treatment, we introduced two alleged medical creams that did not contain any active ingredient and provided different value information by labeling one cream as cheap and the second one as expensive. To support the cheap versus expensive impression, we designed two paper medical-cream boxes that contained design elements for expensive (blue box) and cheap (orange box) medication, respectively (Fig. 1A). A sample of 66 participants that did not take part in the placebo and value-manipulation experiment estimated actual pharmacy prices of the creams on the basis of the appearance of the boxes. The price of the blue box was estimated to be significantly higher than the price of the orange box (Fig. 1B; for statistical

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Marketing features and nocebo effects

- Cheap nocebo
- Expensive nocebo

Cheap group



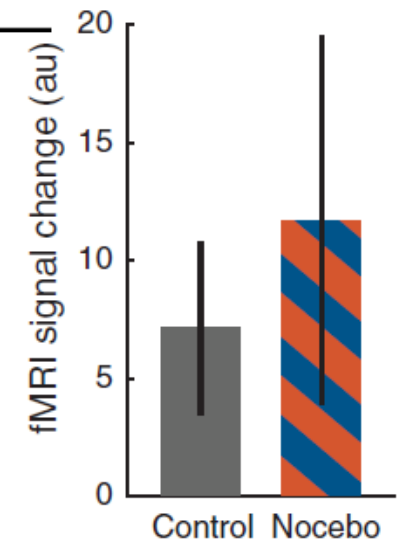
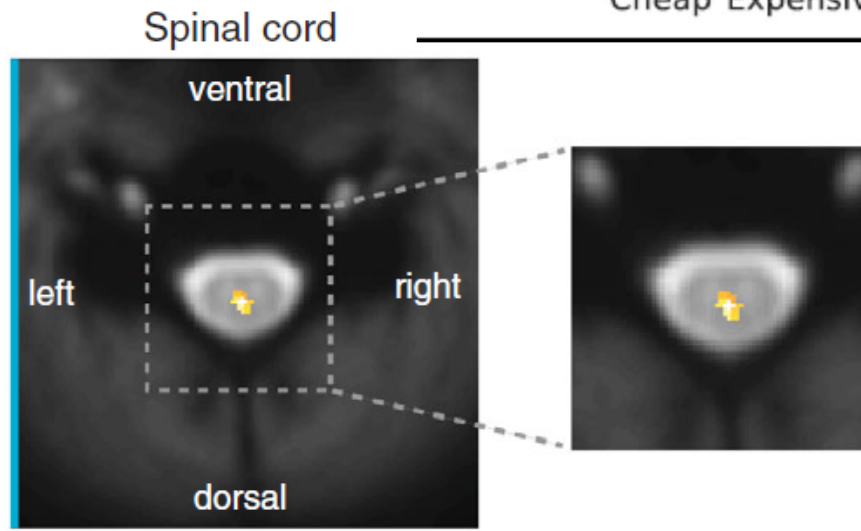
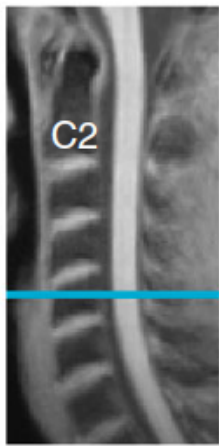
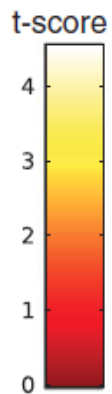
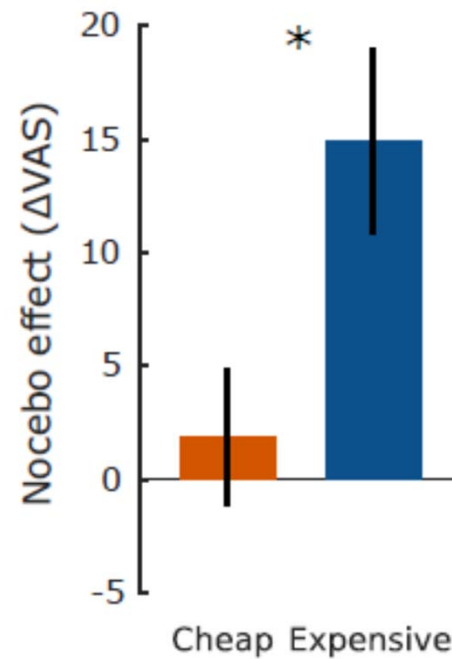
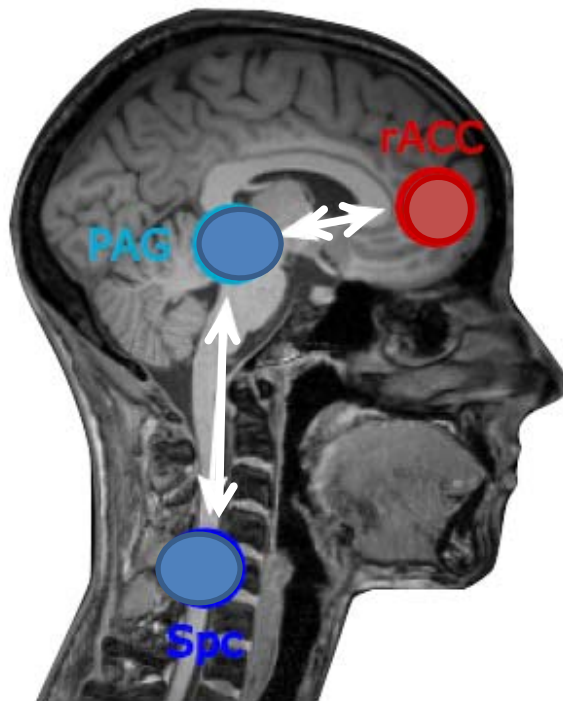
N = 24

Expensive group



N = 25

The rACC-PAG-spinal cord axis and the placebo effect



Tinnermann A, Science. 2017 Oct 6;358(6359):105-108. doi: 10.1126/science.aan1221.

Nocebo effects can make you feel pain

Negative expectancies derived from features of commercial drugs elicit placebo effects

By **Luana Colloca**

The mysterious phenomenon known as the placebo effect describes negative expectancies. This is in contrast to positive expectancies that trigger placebo effects (1). In evolutionary terms, placebo and placebo effects coexist to favor perceptual mechanisms that anticipate threat and dangerous events (placebo effects) and promote appetitive and safety behaviors (placebo effects). In randomized placebo-controlled clinical trials, patients that receive placebos often report side effects (placebos) that are similar to those experienced by patients that receive the investigational treatment (2). Information provided during the informed consent process and divulgence of adverse effects contribute to placebo effects in clinical trials (1). Placebo (and placebo) ef-

ferential placebo effects between the expensive and cheaper treatments. Expectancies of higher pain-related side effects associated with the expensive cream may have triggered a facilitation of nociception processes at early subcortical areas and the spinal cord [which are also involved in placebo-induced reduction of pain (8)]. The rACC showed a deactivation and favored a subsequent activation of the PAG and spinal cord, resulting in an increase of the nociceptive inputs. This suggests that the rACC-PAG-spinal cord axis may orchestrate the effects of pricing on placebo hyperalgesia.



The anticipation of painful stimulation makes healthy study participants perceive nonpainful and low-painful stimulations as painful and high-painful, respectively (9). Verbally induced placebo effects are as strong as those induced through actual exposure to high pain (9). More-

administration was interrupted (13). These findings provide evidence that communication of treatment discontinuation might, at least in part, lead to placebo effects with aggravation of symptoms.

In placebo-controlled clinical trials, placebo effects can influence patients' clinical outcomes and treatment adherence. It was shown in a clinical trial that atorvastatin induced in the same individuals an excess rate of muscle-related adverse events in the non-blinded (i.e., patients knew they were taking atorvastatin), nonrandomized 3-year follow-up phase but not in the initial blinded 5-year phase when patients and physicians were unaware of the treatment allocation (atorvastatin or placebo) (14). Furthermore, misleading information about side effects for statins via public claims has led to treatment discontinuation and an increase in fatal strokes and heart attacks (14).

Given that placebo effects contribute to perceived side effects and may influence clinical outcomes and patients' adherence to medication, we should consider how to avoid

Psychological mechanisms of placebo effects

*Verbal
suggestions*



Conditioned nocebo effects in infants



Full-term infants of diabetic mothers showed more pain than normal infants during venipuncture for newborn screening

- Anticipatory pain behaviors were observed during the cleaning phase (prior to injection), suggesting that skin cleaning repetitively associated with venipuncture, became a conditioned stimulus triggering pain reactions

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Informing patients and clinicians about side effects

- ✓ In RCTs, treatment labels and advertisements can induce placebo effects that influence patients clinical outcomes and treatment adherence
- ✓ A recently published large Lipid-Lowering Arm of the Anglo-Scandinavian Cardiac Outcomes Trial showed that 10 mg open label *atorvastatin* and *placebo* induced an excess rate of muscle-related adverse events in the non-blinded non-randomized three year follow-up phase
- ✓ During the initial five year blinded randomized phase with patients and physicians unaware of the adverse events via public claims did not have the large proportion of muscle-related adverse events that the effects are related to placebo rather than the atorvastatin.

Changes in antidepressant use and suicidal behavior after FDA warnings and media coverage

Objective: To investigate if the widely publicized warnings in 2003 from the US Food and Drug Administration were associated with changes in antidepressant use, suicide attempts, and completed suicides among young people

Results: Trends in antidepressant use changed abruptly after the warnings. In the second year after the warnings, relative changes in antidepressant use were:

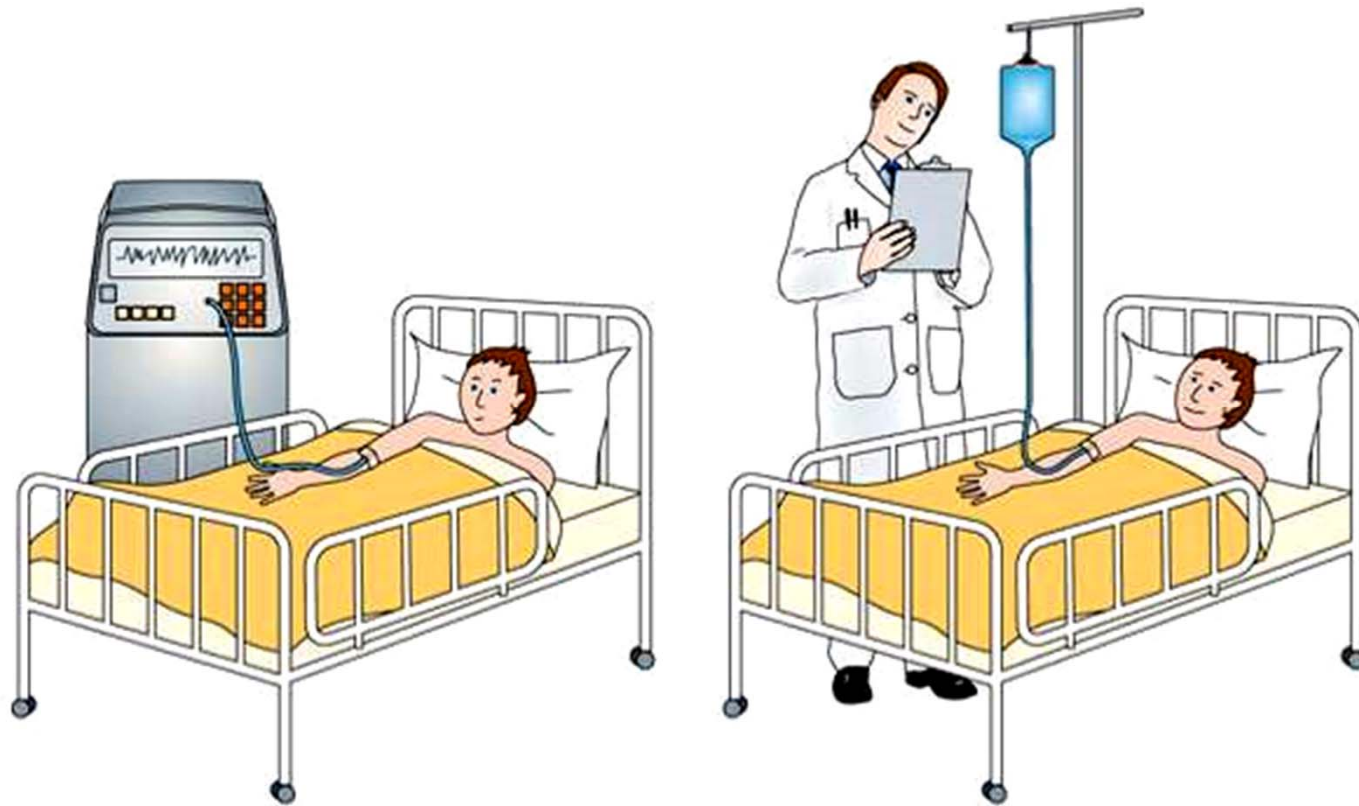
- ✓ -31.0% (95% confidence interval -33.0% to -29.0%) among adolescents
- ✓ -24.3% (-25.4% to -23.2%) among young adults
- ✓ -14.5% (-16.0% to -12.9%) among adults.

Changes in antidepressant use and suicidal behavior after FDA warnings and media coverage

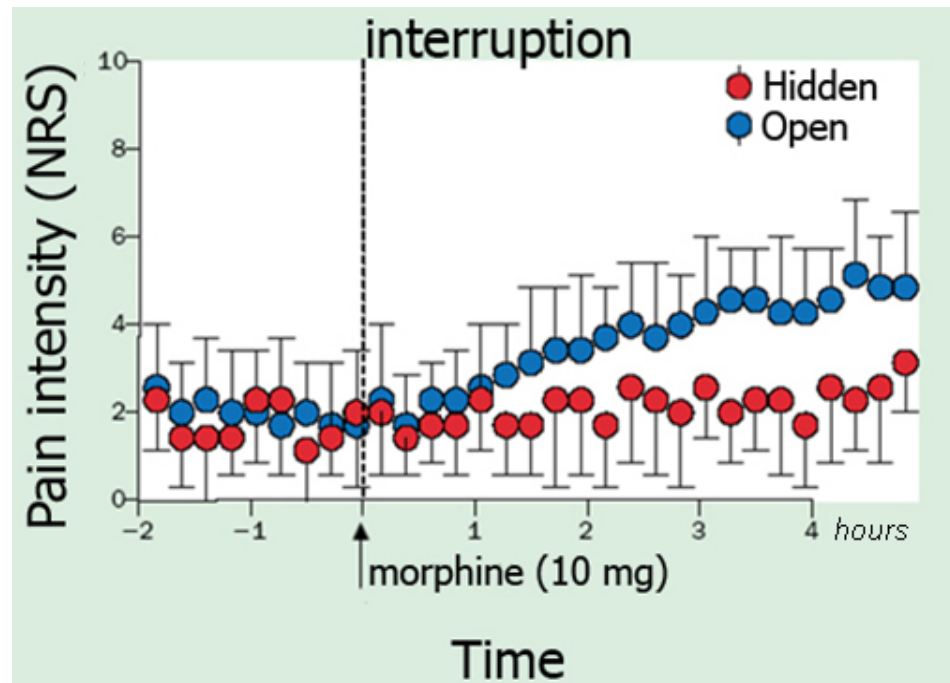
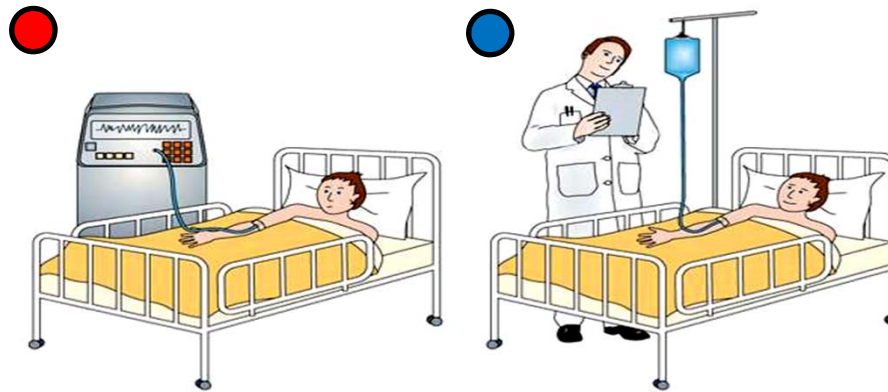
Results: Simultaneously, there were significant, relative increases in psychotropic drug poisonings in adolescents (21.7%) and young adults (33.7%) but not among adults (5.2%). Completed suicides did not change for any age group.

Discussion: ...it is disturbing that after the health advisories, warnings, and media reports about the relation between antidepressant use and suicidality in young people, we found substantial reductions in antidepressant treatment... It is essential to monitor and reduce possible unintended effects of FDA warnings and media reporting.

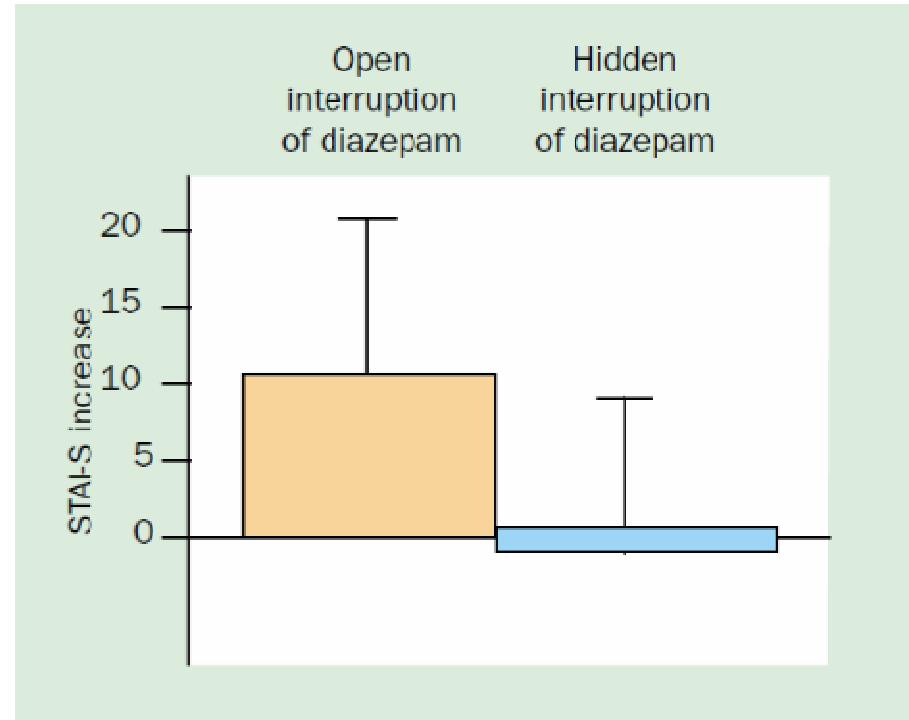
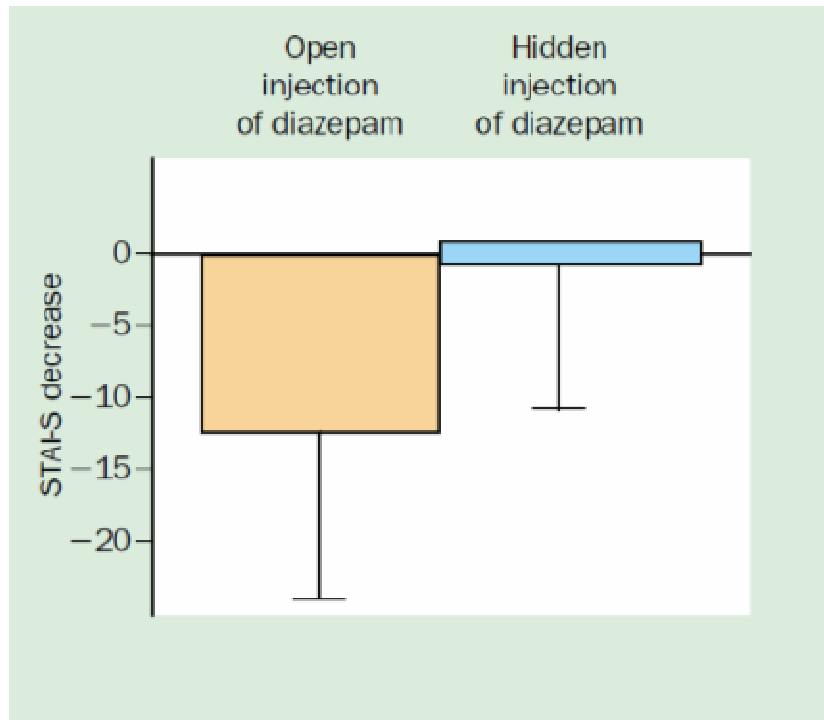
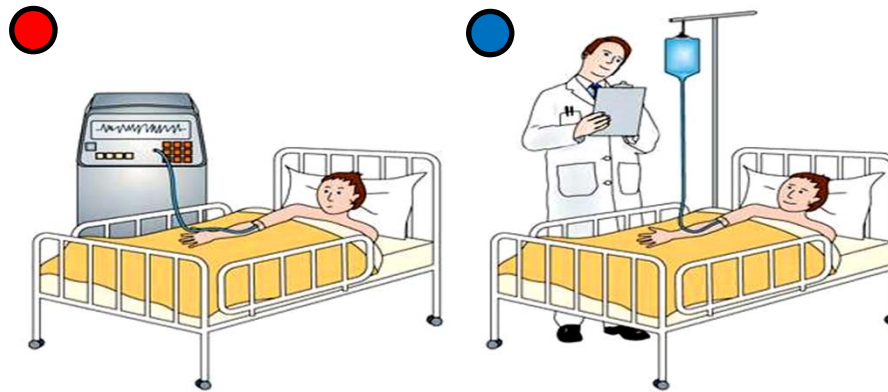
Nocebos and contextual effects



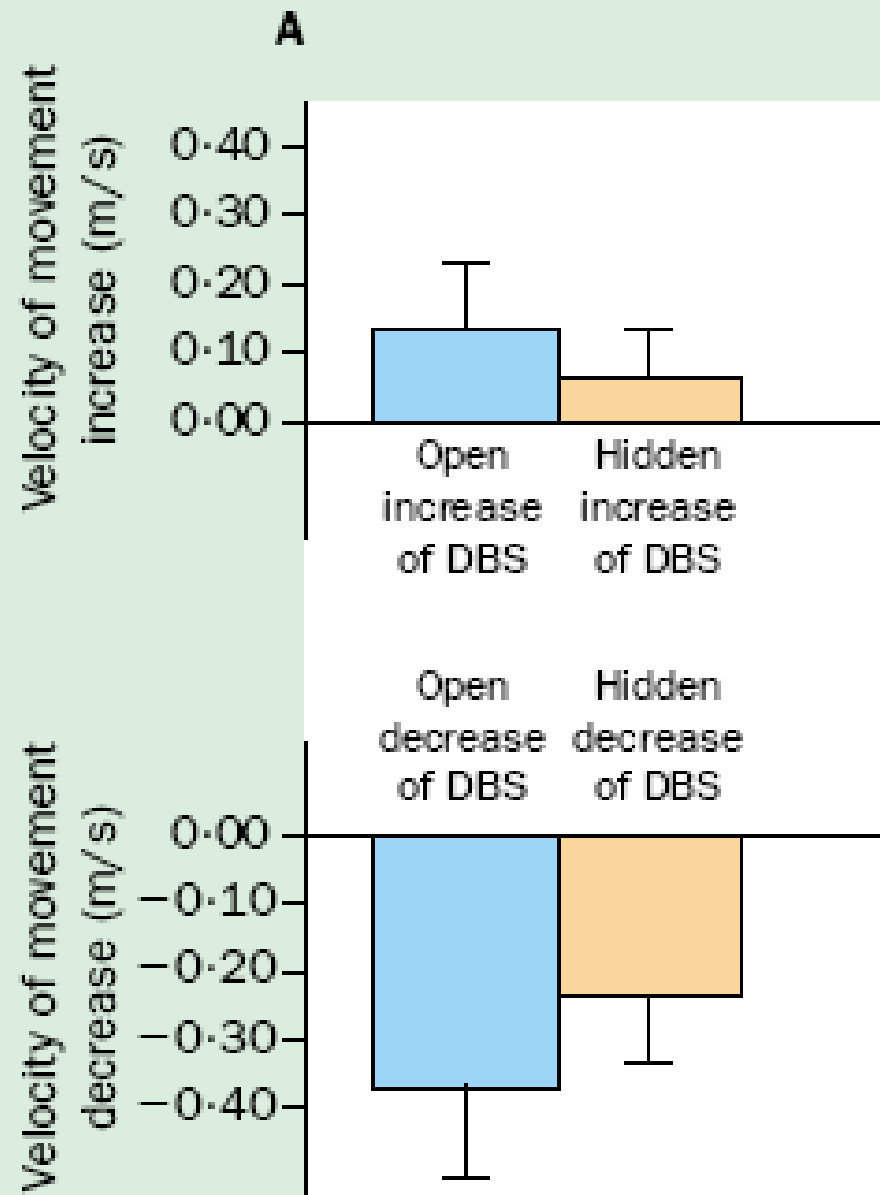
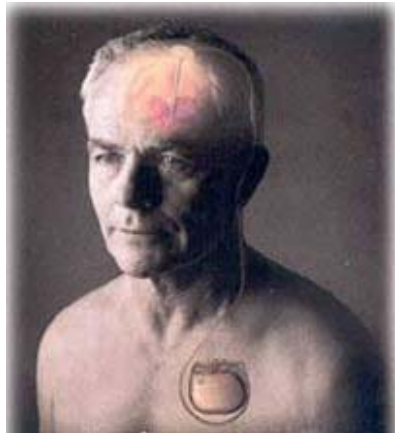
Covert vs overt morphine *interruption*



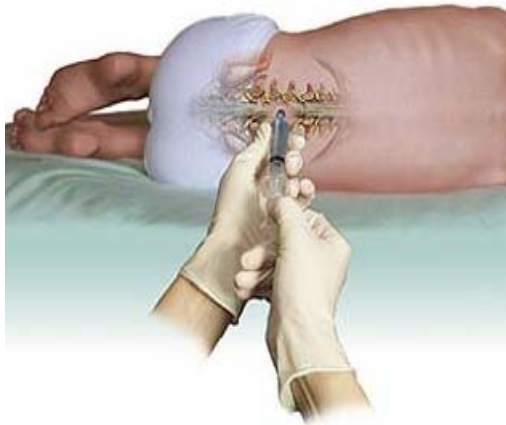
Covert vs overt diazepam *interruption*



Open-hidden paradigm and Parkinson's disease



Negative expectations and HEADACHE



Of the **15** subjects receiving lumbar puncture those who were told to expect a headache afterwards, **7** experienced headaches

Of the **13** subjects who were NOT warned, none experienced headaches

‘...patients should not be told to expect a headache, as this may be a self-fulfilling prophecy’.

Daniels and Sallie, Lancet 1981;1(8227):1003

Nocebo effects in patients with benign prostatic hyperplasia (BPH)

Drug: 5 mg finasteride described as “a compound of proven efficacy for the treatment of BPH”

- Disclosure: **Group 1**: “...it may cause erectile dysfunction, decreased libido, problems of ejaculation but these are uncommon”

Group 2 was not warned about the side effects

- A 6- and 12-months of blinded follow-up revealed a significantly higher proportion of sexual side effects in **Group 1** (43.6%), as compared to **Group 2** with those who were not informed (15.3%)

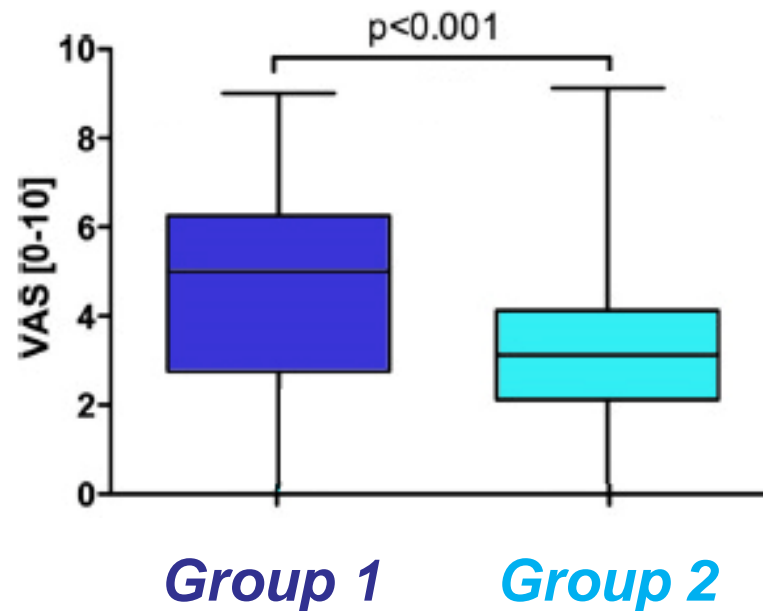
Mondaini et al. J Sex Med 2007;4:1708-1712

CONUNDRUM

A distinctive dilemma for clinicians...

- Clinicians have an obligation to convey truthful information to patients so that they can make informed decisions in light of their preferences and values
- Rather than merely informing patients about specific side effects, clinicians should incorporate in their communication positive frames

Nocebo effects during labor epidural anaesthesia



Group 1: *“You are going to feel a big bee sting; this is the worst part of the procedure”*

Group 2: *“We are going to give you a local anesthetic that will numb the area and you will be comfortable during the procedure”*

Nocebo Effects, Patient-Clinician Communication, and Therapeutic Outcomes

February 8, 2012, Vol 307, No. 6 >

Luana Colloca, MD, PhD; Damien Finniss, MSc Med

- **Reframe** the disclosure process, pay continued attention to ethical approaches surrounding disclosure
- **Educate** clinicians and patients about the possible detrimental effects of nocebo processes
- **Ensure** adequate time and privacy by eliciting patients' perspectives and expectations

How to reduce nocebo effects...

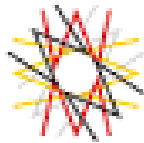
Nocebo effects can be reduced by

- ✓ tailoring patient-clinician communication to balance truthful information about adverse events with expectations of outcome improvement
- ✓ exploring patients' treatment beliefs and prior negative therapeutic history
- ✓ paying attention to framing (ie, treatment description) and contextual effects (ie, price).

What we have learned...

- ✓ Prior experiences, labeling and marketing, patients' and providers' expectancies are processed contributing to the occurrence of placebo effects
- ✓ Further translational research is needed to better handle unwanted placebo effects in daily clinical practice and randomized clinical trials
- ✓ Nurses, pharmacists, and physicians may find this information relevant to daily clinical practice, education and research.

Thank you



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