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Manipulating Human Memory Through Reconsolidation: Stones Left Unturned

Gabriel Lázaro-Muñoz, PhD, JD, MBE and

University of North Carolina and Baylor College of Medicine

Lorenzo Diaz-Mataix, PhD

New York University

Memory reconsolidation is the process by which a previously stored memory, when recalled, becomes unstable and susceptible to modification before being re-stored. Reconsolidation disruption protocols (RDPs) may prove to be powerful therapeutic tools for psychiatric disorders that involve maladaptive learning and memory. However, Elsey and Kindt (2016) present an overly optimistic and incomplete portrayal of the state of reconsolidation research, which leads them to minimize scientific and ethical apprehensions about manipulating human memory through reconsolidation. This is problematic because their depiction of reconsolidation research could mislead stakeholders—such as clinicians, patients, and health policymakers—when evaluating the potential harms and benefits of translating RDPs to the clinical context. We address three pressing concerns about the authors’ depiction of reconsolidation research: 1) insufficient and contradictory evidence about the effectiveness or clinical utility of propranolol RDPs; 2) risk for extemporaneous translation of propranolol RDP research to clinical practice; and 3) lack of discussion of other kinds of RDPs that generate significant ethical challenges—it is necessary to consider different kinds of RDPs when drawing conclusions about the ethics of a topic as broad as “manipulating human memory through reconsolidation.”

EFFECTIVENESS OR CLINICAL UTILITY OF PROPRANOLOL RDPs IN PATIENTS

Elsey and Kindt start their analysis with a title that refers to the manipulation of human memory through reconsolidation as a “new *therapeutic* approach.” The use of the term *therapeutic* suggests there is enough research to support the clinical utility of RDPs. However, studies that have examined the effectiveness of propranolol RDPs in reducing physiologic responses, symptoms, or diagnosis of psychiatric disorders, such as post-traumatic stress disorder (PTSD), have had: mixed findings, small sample sizes, often employed different RDPs, and most lacked critical control groups necessary to rule out the effect of propranolol without memory reactivation (see Table 1). Furthermore, most of the studies that have found a significant effect of propranolol RDPs in patients had samples that were largely composed of women (68% – 91%).

Notably, the most recent propranolol reconsolidation study with PTSD patients (Wood et al. 2015) failed to replicate the findings of Brunet et al. 2008, one of three studies cited by Elsey and Kindt to support the idea that propranolol RDPs could reduce symptoms of PTSD

(Elsey and Kindt 2016, 8–9). Wood et al. 2015—which has the same corresponding author (Dr. Roger K. Pitman) as Brunet et al. 2008—was conducted with a sample of male veterans and included a no-reactivation propranolol group, a control group that was not included in previous PTSD studies. Wood and colleagues did not find significant differences in PTSD symptoms or physiologic responses between the propranolol + memory reactivation group and the propranolol + no-reactivation group when tested a week after the propranolol RDP or propranolol no-reactivation session. These researchers suggest that “non-specific effects of propranolol (i.e., effects unrelated to traumatic memory reactivation) could have lowered the physiological responses in both groups,” and that the sample composed entirely of male participants could also help explain why the Brunet et al. 2008 reconsolidation findings were not replicated (Wood et al. 2015, 35).

Elsey and Kindt also suggest that Wood et al., 2015 did not replicate previous reconsolidation findings because the sample was composed of male participants (Elsey and Kindt 2016, 8–9). This potential explanation to Wood and colleagues’ findings, simply raises more questions about the effectiveness of propranolol RDPs in patients. Are the differences between women and men simply due to the fact that the number of subjects examined in these studies is too small (see Table 1) to observe a significant effect on men? Is the effect found in studies with samples composed mostly of women false and will be eventually refuted by large randomized controlled trials?

In recent years, there is increased awareness about the importance of raising the evidence bar when referring to emerging approaches as therapeutic or adopting new medical practices. Prasad and colleagues surveyed the articles published between 2001 and 2010 in the New England Journal of Medicine. In 40.2% of the articles that examined established medical practices, the current standard of care was found to be ineffective or no better than a previous medical practice (Prasad et al. 2013). Patients and the medical system are exposed to severe harms when insufficiently researched approaches are adopted in medical practice and later proved ineffective, so we should be cautious about the level of evidence we require to refer to emerging technologies as therapeutic. Dr. John P.A. Ioannidis has written extensively about why many biomedical research findings prove to be false (Ioannidis 2005) and two of the problems he identifies are small sample sizes, and bias—even if unintentional—in study designs (e.g., gender composition of samples), both of which are an issue with the current state of reconsolidation research with patients. Elsey and Kindt do acknowledge that “a large, randomized controlled trial with participants representing both genders and a range of PTSD etiologies would help assess the viability” of propranolol RDPs (Elsey and Kindt 2016, 9). However, we believe that both their portrayal of the state of reconsolidation research and referring to human memory manipulation through reconsolidation as a “new *therapeutic* approach” may unintentionally mislead readers regarding the current limitations of our knowledge about reconsolidation, particularly with patients.

RISK OF EXTEMPORANEOUS TRANSLATION OF PROPRANOLOL RDP RESEARCH TO CLINICAL PRACTICE

Balanced and careful discussion of the evidence is particularly important in this context because propranolol is approved by the United States Food and Drug Administration (FDA) for other purposes, but not “reconsolidation-based treatments.” However, FDA does not have authority to regulate medical practice. Therefore, in the United States, few regulatory and legal obstacles can impede clinicians from currently using propranolol off label to try RDPs with patients suffering from traumatic memories.

From a legal and medical standpoint, propranolol RDPs are not the standard of care for treating PTSD or any other psychiatric disorder. This may lead some to believe that clinicians would currently be held liable for any harm patients may suffer from the use of propranolol RDPs in the clinic. However, courts often show deference to clinicians when it comes to off-label prescriptions and reasonable medical innovations, especially when the standard of care does not meet a patient’s medical needs, and the clinician can point to some research that supports the innovation (Mehle 2015, 446–51). Patients could benefit from this because it allows clinicians to depart from the standard of care in search for potentially effective innovations. However, this regulatory and legal reality accentuates the responsibility we have as scientists and bioethicists to present the harms, benefits, and limitations of emerging medical technologies in a balanced way that will help clinicians and other stakeholders avoid the extemporaneous translation of emerging technologies to the clinical setting.

OTHER RDPs RAISE SIGNIFICANT ETHICAL CHALLENGES

Although the authors warn at the beginning of their article that due to space limitations they will emphasize on behavioral and propranolol RDPs, which are the focus of their lab (Elsey and Kindt 2016, 3), they go on to make sweeping conclusions about the ethical challenges posed by “reconsolidation-based memory modification” (Elsey and Kindt 2016, 12–17). There is evidence to suggest that RDPs may be effective in disrupting appetitive, motor, episodic, and spatial memories in humans. RDPs for appetitive memories are currently being tested to examine their effectiveness for reducing symptoms of substance-related and addictive disorders. These RDPs can pose significant ethical challenges. For example, some drug abuse RDPs involve the presentation of cocaine cues which elicit cravings in participants with cocaine dependence (Saladin et al 2013). Eliciting drug cravings for a RDP in patient-participants who suffer from drug addiction could prove effective in reducing drug use, but generates significant ethical concerns about the harms that may be caused to those individuals who do not respond effectively to these RDPs. Furthermore, studies with rodents and humans suggest that the presentation of an unconditioned stimulus (US) is another effective trigger for RDPs (Díaz-Mataix et al. 2011). In fact, it is possible that triggering reconsolidation by presenting a US (e.g., actual cocaine use for patients with cocaine dependence) may achieve a more complete reactivation of the maladaptive memory and could produce a more robust RDP effect, than if only a cue associated with the traumatic event or drug of abuse is presented. These, like other types of RDPs will generate significant

ethical challenges, therefore, it is important to phrase conclusions about the ethics of RDPs with reference to the protocols analyzed.

RDPs may prove to be powerful therapeutic tools. Nevertheless, it is essential to more fully acknowledge the limitations of the state of reconsolidation research and educate stakeholders about these. This will allow stakeholders to make well-informed decisions about whether, when, and how to translate these technologies, and identify what kind of risks and benefits should be disclosed to patients so they can provide ethically sound and legally valid informed consent if any RDP is ever adopted in clinical practice.

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TABLE 1

Studies examining propranolol RDPs in patients with pathological traumatic memories or phobia *

Study and Population	Groups and Sample Sizes
Brunet et al. 2008 Patients with chronic PTSD (68% women)	(Group 1) 9 participants received propranolol after one memory reactivation session (Group 2) 10 participants received placebo after one memory reactivation session
Brunet et al. 2011 [†] Patients with chronic PTSD (See specific studies within this publication for the relative frequency of gender in each sample)	Study 1: One group of 28 participants (68% women) received propranolol before each of six memory reactivation sessions; no control groups Study 2: One group of 7 participants (71% women) received propranolol before each of six memory reactivation sessions; no control groups Study 3: (Group 1) 7 participants (71% women) received propranolol before each of six memory reactivation sessions (Group 2) 25 participants (48% women) refused propranolol, but served as a control group in which PTSD symptoms were measured at similar time points as Group 1
Poundja et al. 2012 [†] Patients with chronic PTSD (70% women)	One group of 33 participants received propranolol before each of six memory reactivation sessions; no control groups
Brunet et al. 2014 Patients with PTSD (68% women)	One group of 28 participants (22 included for analysis) received propranolol before each of six memory reactivation sessions; no control groups, but the results of this group were compared to the results of the two groups in Brunet et al. 2008
Wood et al. 2015 Patients with chronic PTSD (100% male veterans)	(Group 1) 10 participants received propranolol before one memory reactivation session (Group 2) 8 participants received propranolol but no memory reactivation session
Soeter and Kindt 2015 [†] Patients with Arachnophobia (91% women)	(Group 1) 15 participants received propranolol after one tarantula exposure session (Group 2) 15 participants received placebo after one tarantula exposure session (Group 3) 15 participants received propranolol but no tarantula exposure session

* Menzies 2012 examined the effectiveness of a propranolol RDP in 36 participants (63.9% males) and found a decrease in different PTSD-related measures, but the study sample combined PTSD and subsyndromal PTSD participants, and had a number of other methodological problems. We encourage readers to examine the methods of this and all the other studies on this table.

[†] For reference, please see Elsey and Kindt 2016