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## Optimizing the efficacy of exposure in PTSD treatment

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Both prolonged exposure (PE) and eye movement desensitization reprocessing (EMDR) are recommended in international guidelines as first choice treatments in PTSD patients. Its efficacy is shown in many randomized controlled trials and several meta-analytic reviews (Powers, Halpern, Ferenschak, Gillihan, & Foa, 2010). The proposed working mechanism in PE is fear extinction by effective emotional processing of traumatic memories. Notwithstanding the efficacy of PE, there is room for improvement. Many patients remain symptomatic after treatment (Schnurr et al., 2007), and dropout-rates are substantial and vary between 20 and 35% (Schnurr et al., 2014). Previous studies showed that adding psychological interventions to PE did not succeed in increasing effect-sizes compared to stand-alone PE (Kehle-Forbes et al., 2012). An alternative way to enhance PE efficacy is the combination with pharmacological treatment such as antidepressants, or oxytocin (see this issue: Olff et al., 2015). However, empirical data regarding the efficacy of combining PE with antidepressants are scarce. Additionally, the reported efficacy of adding antidepressants to PE varied between nil and modest compared to PE as stand-alone treatment (De Kleine, Rothbaum, & Van Minnen, 2013; Marshall et al., 2007; Rothbaum et al., 2006; Simon et al., 2008). On the other hand, compared to PE and EMDR the efficacy of pharmacological treatment as stand-alone in PTSD patients is likewise modest (Ipser, Seedat, & Stein, 2006; Watts et al., 2013). Approximately a decade ago an interesting new direction emerged. Fundamental research showed pharmacological enhancement of the underlying mechanisms in exposure therapy: extinction learning and reconsolidation (Debiec & Ledoux, 2004). Although the interrelation between extinction learning and reconsolidation is not fully understood, it is clear that these mechanisms are underlying the efficacy of exposure therapy (Kindt & Soeter, 2013). The findings in fundamental research were translated to clinical studies in anxiety disorders. As fear extinction is linked to the *N*-methyl-D-aspartate (NMDA) glutamatergic receptor activity in the basolateral amygdala, these studies focused on pharmacological enhancement of exposure therapy by NMDA receptor agonists, for instance D-cycloserine (DCS), patients with specific phobia, social anxiety disorder, panic disorder, and obsessive compulsive disorder (Bontempo, Panza, & Bloch, 2012; Norberg, Krystal, & Tolin, 2008). Studies in posttraumatic stress disorder were lacking. Therefore, we conducted a placebo-controlled randomized trial of DCS-enhancement PE treatment in a heterogeneous PTSD population ( $n=67$ ). Although initially DCS-enhancement showed no difference compared to the placebo-group, we found that DCS enhanced PE treatment in a subgroup of patients with more severe PTSD at baseline and an initial non-response on PE (De Kleine, Hendriks, Kusters, Broekman, & Van Minnen, 2012). Furthermore, our results support the influence of personality traits on outcome. High consciousness and low extraversion predicted a better response in the DCS-enhancement treated patients compared to the placebo-group (De Kleine, Hendriks, Smits, Broekman, & Van Minnen, 2014). However, the results of DCS-enhancement in additional PTSD studies are controversial with conflicting results in outcome (Difede et al., 2014; Litz et al., 2012; Rothbaum et al., 2014). The proposed DCS-enhancement in exposure therapy as a one-size-fits-all enhancement strategy is unequivocally too optimistic.

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