Journal of Psychiatric Research 45 (2011) 1042–1047

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

D-Cycloserine does not improve but might slightly speed up the outcome of in-vivo exposure therapy in patients with severe agoraphobia and panic disorder in a randomized double blind clinical trial

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ARTICLE INFO

Article history:
Received 1 November 2010
Received in revised form
30 January 2011
Accepted 31 January 2011

Keywords:
Pharmacological augmentation
CBT
Panic disorder
Agoraphobia
Flooding

ABSTRACT

D-cycloserine (DCS) – augmented exposure therapy has proven efficacy in the treatment of acrophobia, social phobia, panic disorder and OCD. Here we studied whether DCS can also improve the effect of cognitive behavioral therapy (CBT) in patients with agoraphobia and panic disorder. To this end, 39 patients with the diagnoses of agoraphobia and panic disorder were treated with 11 sessions of CBT including three individual in-vivo exposure sessions (flooding), augmented with either 50 mg of DCS ($N = 20$) or placebo ($N = 19$) in a randomized double blind design. Primary outcome was the total score of the panic and agoraphobia scale. Both groups profited considerably from therapy and DCS did not significantly improve this outcome ($p = 0.475$; $\eta^2_p = 0.01$). However, there was a statistical trend ($p = 0.075$; $\eta^2_p = 0.17$) in the more severely ill patients that DCS accelerated symptom reduction in the primary outcome at post-therapy. No serious adverse effects occurred during the trial. We conclude that in patients with agoraphobia and panic disorder, DCS seems to lack an additional benefit to efficient cbt, probably due to a floor effect. Nonetheless, the acceleration of symptom reduction in severely ill patients might represent a valuable treatment option deserving further investigation.

1. Introduction

The pharmacological augmentation of cognitive behavioral therapy is a new and promising strategy in the treatment of anxiety disorders. D-cycloserine (DCS) indirectly increases glutamatergic transmission via the strychnine-insensitive glycin binding site of the *N*-methyl-D-aspartat (NMDA) receptor. The drug shows no anxiolytic properties but improves NMDA dependent extinction learning if administered before or up to 60 min after extinction training in fear conditioning paradigms in rodents (Ledgerwood et al., 2003; Walker et al., 2002). In contrast, without extinction training DCS administration has no effect on fear responses to the conditioned stimulus. After systematic studies in preclinical research, this effect has subsequently been tested in clinical studies employing exposure therapy which is considered to be equivalent to extinction training. DCS has been shown to improve the effects of situational exposure therapy in acrophobia (Ressler et al., 2004), social phobia (Hofmann et al., 2006; Guastella et al., 2008) and to a smaller extend in OCD (Kushner et al., 2007; Wilhelm et al., 2008). It also facilitated the effect of a group cognitive behavioural treatment with interoceptive exposures (exposure to evoked body sensations) in $n = 27$ patients with a panic disorder (Otto et al., 2010). In contrast, it lacked efficacy if administered to patients with PTSD without exposure treatment (Heresco-Levy et al., 2002), to subjects with non-clinical spider fear (Guastella et al., 2006) or to healthy subjects in fear conditioning and extinction paradigms (Guastella et al., 2007; Kalisch et al., 2009). Grillon (2009) suggests that healthy subjects employ higher cognitive strategies of emotion regulation in common fear conditioning paradigms, while the effect of DCS on extinction learning becomes relevant only in situations of strong fear as existent in clinical anxiety.

This study investigated the potential of DCS to improve the effect of cognitive behavioral therapy including in-vivo exposures (flooding) to avoided real-life situations in patients with agoraphobia that also suffered from panic disorder.

2. Materials and methods

2.1. Patients

About 1000 out-patients were screened by telephone and about 200 of them invited for thorough psychiatric and somatic diagnostics

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doi:10.1016/j.jpsychires.2011.01.020

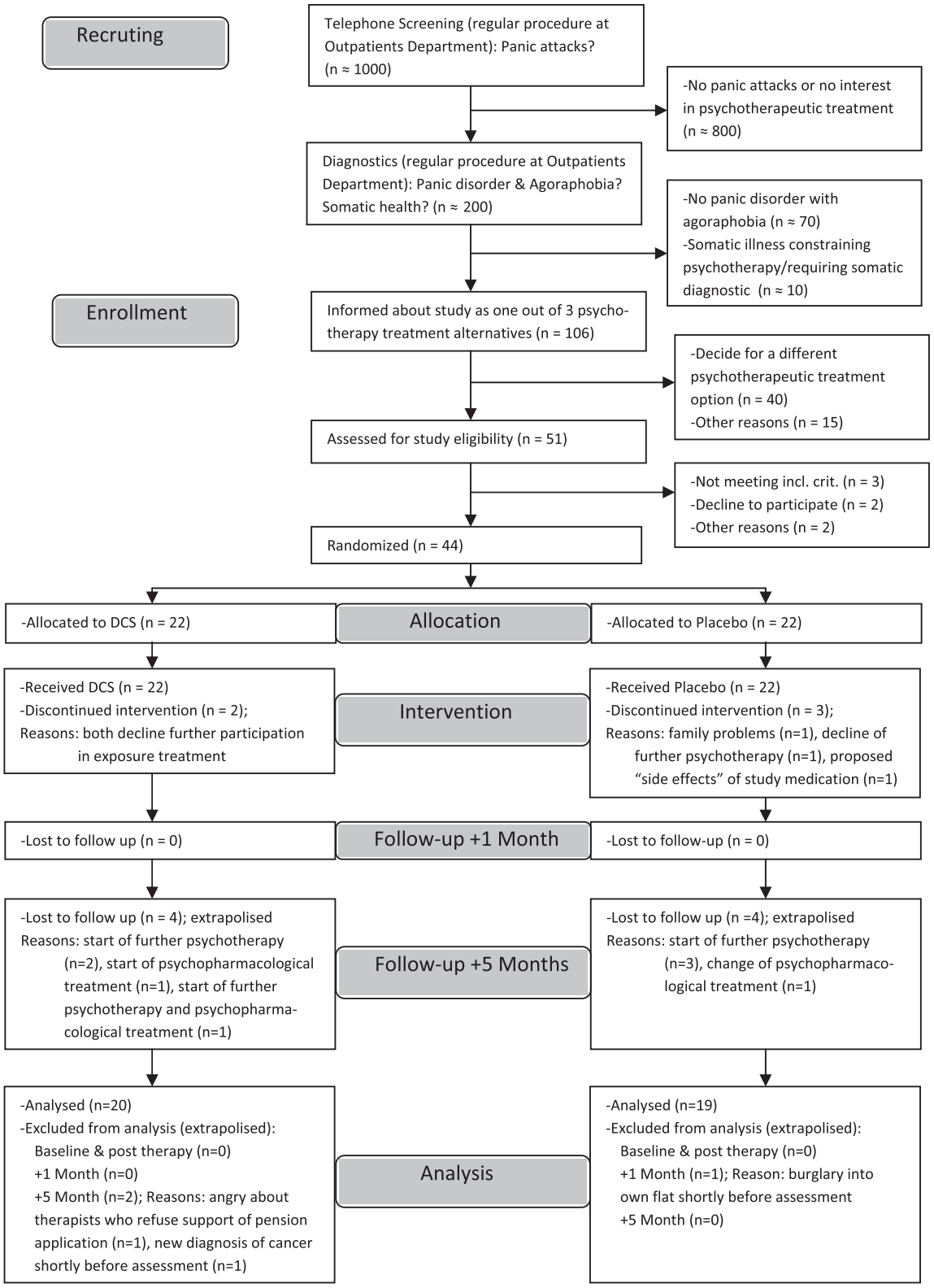

Fig. 1. Participant flow for the primary outcome panic and agoraphobia scale.

as part of the regular procedure in our out-patients department. If they met criteria of panic disorder, agoraphobia and somatic health, they were offered participance in the D-cycloserine psychotherapy study as one of several psychotherapy treatment alternatives. 51 patients with the diagnoses of panic disorder and agoraphobia consented and after further study-specific diagnostics 44 patients were randomised to either DCS ($n = 22$) or placebo ($n = 22$), for details see Fig. 1. Psychiatric diagnoses were determined by a semi-