Atomoxetine for hoarding disorder: A pre-clinical and clinical investigation

Giacomo Grassi a, b, *, Laura Micheli c, Lorenzo Di Cesare Mannelli c, Elisa Compagno a, Lorenzo Righi d, Carla Ghelardini c, Stefano Pallanti a, b

a University of Florence, Department of Neuroscience, Psychology, Drug Research and Child Health, Neurofarba, via delle Gore 2H, 50141, Florence, Italy
b Institute of Neuroscience, via La Marmora 24, 50121, Florence, Italy
c Department of Neuroscience, Psychology, Drug Research and Child Health, Neurofarba, Pharmacology and Toxicology Section, University of Florence, Florence, Italy
d University of Siena, Department of Molecular and Developmental Medicine, Siena, Italy

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Abstract

Despite several studies suggested that inattention and impulsivity-compulsivity could represent two core dimensions of hoarding disorder (HD), only a small case series study investigated the effectiveness of attention-deficit-hyperactivity-disorder (ADHD) medications in HD. The aim of the present study was to target attentional and inhibitory control networks in HD patients through the ADHD medication atomoxetine, moving from a preclinical investigation on an animal model of compulsive-like behavior (marble burying test) to a clinical investigation on both medicated and unmedicated patients with a primary diagnosis of HD without ADHD. Our preclinical investigation showed that acute administration of atomoxetine significantly reduced the compulsive-like behaviours of mice in the marble burying test without affecting neither locomotor activity and coordination nor exploration behaviours. When compared, atomoxetine and fluoxetine showed similar effects on the marble burying test. However, fluoxetine impaired both locomotor and exploratory activity. In our clinical investigation 12 patients were enrolled and 11 patients completed an open trial with atomoxetine at flexible dose (40–80 mg) for 12 weeks. At the endpoint the mean UCLA Hoarding Severity Scale score decreased by 41.3% for the whole group (p = 0.0003). Six patients were classified as full responders (mean symptom reduction of 57.2%) and three patients as partial responders (mean symptom reduction of 27.3%). Inattentive and impulsivity symptoms showed a significant mean score reduction of 18.5% from baseline to the endpoint (F (1,9) = 20.9, p = 0.0013). Hoarding symptoms improvement was correlated to reduction of patients’ disability and increased in their global functioning. These preclinical and clinical data suggest that atomoxetine may be effective for HD and therefore should be considered for future controlled trials.

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1. Introduction

Hoarding disorder (HD), newly included disorder in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5, APA, 2013), is characterized by persistent difficulty in parting with possessions, which results in severely cluttered living spaces, distress, and impairment (Mataix-Cols, 2014). Up to 90% of persons with hoarding engage in excessive acquisition of items that they do not need or for which no space is available (Mataix-Cols, 2014). Recent epidemiological studies estimated a prevalence around 1.5% in the general population (Nordsletten et al., 2013) and several studies showed that hoarding disorder substantially affects quality of life, family relationships and can pose a range of health risks and poor sanitation (Saxena et al., 2011; Tolin et al., 2008a, 2008b, Frost et al., 2000).

Once considered a variant of OCD, hoarding disorder is now included as a separate disorder in the DSM-5 due to unique neurobiological and phenomenological characteristics. Despite not included in the DMS-5 criteria, increasing evidence in the last years, suggested that inattention and impulsivity-compulsivity could represent two relevant dimensions of hoarding disorder (Mataix-Cols, 2014). Attentional and memory problems have been
hypothesized to underlie hoarding behaviors since the first hoarding model proposed by Frost and Hartl in 1996 (Frost and Hartl, 1996). This hypothesis came from the observation that individuals who hoard frequently shift attention from an object to another, resulting in an inability to make decisions during tasks such as sorting (Grisham and Barlow, 2005). Several clinical and neurocognitive studies supported the relevance of this link. First of all, attention deficit hyperactivity disorder (ADHD) comorbidity and ADHD symptoms in HD are more frequent than OCD comorbidity (Hall et al., 2013; Hartl et al., 2005). Moreover, a recent study showed that inattention symptoms predict the severity of hoarding core dimensions such as clutter, difficulty discarding, and acquiring (Tolin and Villavicencio, 2011a). Finally, a large epidemiological study showed that childhood inattention (but not hyperactivity) is associated with lifetime hoarding symptoms (Fuliana et al., 2013) and a recent family study showed a common load for inattention and hoarding symptoms (Dijk et al., 2016). Although one study (Sumner et al., 2015) showed normal attentional performance, the majority of data show attentional impairments in HD subjects compared to controls (Mackin et al., 2016; Tolin et al., 2011b, Grisham et al., 2007). In these studies, hoarding patients showed worse performances respect to healthy subjects on sustained attention tasks, visual detection and visual memory tasks (Mackin et al., 2016; Tolin et al., 2011b, Grisham et al., 2007). Three distinct but interconnected networks have been proposed to form the human attention network (Raz and Buhle, 2006; Petersen and Posner, 2012). This network is composed by the alerting network (carrying out stimulus recognition and maintaining a state of alertness), the orienting network (selecting specific information from among multiple sensory stimuli) and the executive network (resolving conflict) (Raz and Buhle, 2006; Petersen and Posner, 2012).

The above-mentioned neurocognitive results in HD subjects, in a Research Domain Criteria (RDoC) perspective, imply a dysfunction of the alerting attention network. This network is involved in sustained attention, vigilance and alertness, it is mainly innervated by noradrenergic projection from the locus coeruleus (Raz and Buhle, 2006; Chamberlain and Robbins, 2013) and it is composed by several right-sided prefrontal (e.g. dorso-lateral prefrontal cortex, anterior cingulate) and parietal areas (inferior parietal cortex) (Raz and Buhle, 2006).

Impulsivity and compulsivity represent two other core aspects of hoarding phenomenology. In fact, excessive acquisition is present in most of hoarding patients and more than 75% of HD patients show an acquisition-related impulse control disorder (compulsive buying, kleptomania, and acquiring free things) (Frost et al., 2011). Furthermore, a recent study on general population showed that both impulsive and compulsive traits are associated with hoarding symptoms (Timpano et al., 2013). These clinical observations are supported by several neurocognitive studies that showed impaired performances of HD patients on stop signal and go/no-go tasks suggesting a dysfunction of the inhibitory control network in HD (Morein-Zamir et al., 2014; Woody et al., 2014). The inhibitory control network is composed by right lateral and medial prefrontal areas (mainly by the right inferior frontal gyrus and the presupplementary motor area) and its functioning seems to be modulated by noradrenergic drugs such as atomoxetine (Chamberlain et al., 2009).

Despite these above-mentioned studies clearly show the relevance of inattention and impulsive-compulsive traits in hoarding disorder, to date only one case-report (Kaplan and Hollandier, 2004) and a small case series on four patients investigated the effectiveness of a FDA-approved medication for ADHD in hoarding patients (Rodriguez et al., 2013). In this small case series 4 patients with hoarding disorder without ADHD comorbidity were treated with methylphenidate extended release. Two of four patients showed an improvement in hoarding symptoms, particularly in the excessive acquisition domain, and all the patients showed an improvement in attention symptoms. However, none of the patients chose to continue taking methylphenidate after study end because of adverse effects (eg, insomnia, palpitations) (Rodriguez et al., 2013).

Current evidence-based options for the treatment of hoarding disorder are very limited. Cognitive-behavioural therapy (CBT) with home visits seems to be the most promising approach. However, a recent meta-analysis found out that HD patients remain significantly symptomatic at post-treatment and CBT has only a moderate effect on excessive acquisition and global impairment (Tolin et al., 2015). Regarding pharmacological interventions, to date only two open trials are available on hoarding patients (Saxena et al., 2014; Saxena and Summer, 2014). These trials investigated the effectiveness of paroxetine and venlafaxine in HD patients and found a mean symptoms reduction of 31% and 36% respectively (Saxena et al., 2007a; Saxena and Summer, 2014). However, the effectiveness of serotonergic drugs is controversial. Several studies in the last ten years and a meta-analysis on OCD trials (in which only OCD patients with hoarding symptoms have been included until the publication of DMS-5) showed that hoarding is correlated to a non-response to serotonergic drugs (Bloch et al., 2014), while a recent meta-analysis that included also the venlafaxine and paroxetine trials on DMS-5 HD patients, suggested that HD patients could be responsive to SRIs (Brakoulas et al., 2015). Thus, the research of new treatment approaches and new treatment targets represents a priority in this field in order to achieve a better outcome.

The aim of the present study was to target attention networks and inhibitory control networks in hoarding disorder assessing the potential effectiveness of atomoxetine, a noradrenaline reuptake inhibitor approved for childhood and adulthood ADHD, moving form a pre-clinical phase to a clinical phase. Indeed, we investigated the atomoxetine effects on an animal model of compulsive-like behaviors (marble burying test) and on both medicated and un-medicated patients with a primary diagnosis of hoarding disorder.

2. Experimental procedures

2.1. Pre-clinical investigation

The aim of the pre-clinical phase was to investigate the acute effects of atomoxetine on an animal model of compulsivity, the marble-burying test. This behavioral test has been widely used to test drugs for obsessive-compulsive disorder and OCD spectrum disorders. Burying behavior in rodents refers to the displacement of bedding material using the snout and forepaws in order to cover an object. Inhibition of object burying was originally suggested as a screening test for anxiolytic activity, but several studies in the last ten years led to the conclusion that marble-burying behavior does not model anxiety, but may rather be related to compulsive behaviors (Albelda and Joel, 2012). The predictability of the marble-burying test after acute drugs administration has been widely demonstrated in research articles (Gawali et al., 2016; Ichimaru et al., 1995; Joel, 2006; Kalariya et al., 2015). Thus, we decided to compare acute effects of atomoxetine on the marble-burying test with its chronic effects on patients with a primary diagnosis of hoarding disorder.

Despite atomoxetine has been previously tested in other impulsivity-compulsivity animal models and showed to reduce impulsivity and compulsivity development in impulsive rats (Ansquer et al., 2014), it has never been tested in the marble-burying test. Moreover, we have choose the marble-burying test because it deserve some phenomenological connection with
hoarding behaviors in humans (e.g. compulsive saving of marbles).

Since this experimental paradigm is strongly related to animal motor capabilities, we assessed the effects of compounds on locomotor activity, exploration behaviors and motor coordination (using the hole-board and rotarod test, respectively). Fluoxetine, a well-established anti-compulsive agent in animal models, was used as comparison.

2.1.1. Animals

Male CD-1 albino mice (Harlan, Varese, Italy) weighing approximately 22–25 g, at the beginning of the experimental procedure, were used. Animals were housed in CeSAL (Centro Stabulazione Animali da Laboratorio, University of Florence) and used at least 1 week after their arrival. Twelve mice were housed per cage (size 26 × 41 cm); animals were fed a standard laboratory diet and tap water ad libitum, and kept at 23 ± 1 °C with a 12 h light/dark cycle, light at 7 a.m. All animal manipulations were carried out according to the European Community guidelines for animal care (D.L. 116/92), application of the European Communities Council Directive of 24 November 1986 (86/609/EEC). The ethical policy of the University of Florence complies with the Guide for the Care and Use of Laboratory Animals of the US National Institutes of Health (NIH Publication No. 85-23, revised 1996; University of Florence assurance number: A5278-01). Formal approval to conduct the experiments described was obtained from the Animal Subjects Review Board of the University of Florence. Experiments involving animals have been reported according to ARRIVE guidelines (Kilkenny et al., 2010). All efforts were made to minimize animal suffering and to reduce the number of animals used.

2.1.2. Behavioral testing

Animals were habituated to the experimental room and randomly assigned to each treatment group. Mice were investigated by observers blinded for treatment of the animals. Ten animals per group were used.

2.1.3. Marble-burying test

The marble-burying behaviour test was performed as described previously (Njung’e and Handley, 1991; Thomas et al., 2009). Briefly, the apparatus consisted of a (21 × 38 × 14 cm) box cage containing 5-cm thick sawdust/fresh hardwood chip bedding. Twenty four small glass marbles (10 mm) were arranged on bedding in the form of an array. Mice were then exposed to marbles individually for 30 min and unburied marbles were counted. A marble was considered to be “buried” if it was covered with sawdust more than 67% (i.e. two-third size). The final outcome was then rated by counting the number of marbles buried. The time that the mouse spent in the corners, the number of rearings and the time of the first buried marble, were also measured. Drugs and vehicle were administered 30 min before the beginning of the test.

2.1.4. Rotarod test

The apparatus consisted of a base platform and a rotating rod of 3 cm diameter with a non-skid surface. The rod was placed at a height of 15 cm from the base. The rod, 30 cm in length, was divided into 5 equal sections by 6 disks. Thus up to 5 mice were tested simultaneously on the apparatus, with a rod rotation speed of 16 r.p.m. The integrity of motor coordination was assessed on the basis of the number of falls from the rod in 30 s.

Measures were performed before and after drugs administration at 15 min intervals. Drugs injections were carried out 30 min before the beginning of the test.

2.1.5. Hole-board test

The locomotor activity was evaluated using the hole-board test. The apparatus consisted of 40 a cm square plane with 6 flush mounted cylindrical holes (3 cm diameter) distributed 4 × 4 in an equidistant, grid like manner. Mice were placed on the center of the board one by one and allowed to move about freely for a period of 5 min each. Two photobeams, crossing the plane from mid-point to mid-point of opposite sides, thus dividing the plane into 4 equal quadrants, automatically signalled the movement of the animals (counts in 5 min) on the surface of the plane (locomotor activity).

2.1.6. Drug administration

Fluoxetine (30 mg kg⁻¹) was dissolved in 0.9% saline and intraperitoneally (i.p.) administered. Atomoxetine (60 mg kg⁻¹) was suspended in 1% carboxymethylcellulose sodium salt (CMC) and per os administered. Control animals were treated with vehicles, no different behavioral effects were induced by saline i.p. or CMC p.o.

2.1.7. Statistics

Results were expressed as mean ± sem. Statistical analysis was performed using One-way ANOVA followed by Bonferroni comparison test. P values of less than 0.05 was considered significant. Data were analysed using the “Origin 9.1” software.

2.2. Clinical investigation

2.2.1. Participants

Participants were recruited from the compulsive and impulsive disorders unit of the University of Florence from November 2014 to November 2015. To be enrolled, participants had to fulfill the DSM-5 diagnostic criteria for hoarding disorder as their primary, most distressing, or impairing condition. All participants were diagnosed by clinical interview, followed by administration of the MINI International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). We excluded patients with a lifetime diagnosis of attention deficit hyperactivity disorder (ADHD) by assessing each patient with the validated Italian version of the DIVA 2.0 (Koijj, 2012; the Italian version by Salerno and Pallanti, 2013). Patients with primary psychotic disorders, bipolar disorder, panic disorder, post-traumatic stress disorder, substance abuse/dependence, eating disorders, dementia, or intellectual disability were excluded. All medicated participants had to be stable on their ongoing medications since at least 4 weeks before starting the atomoxetine trial. Patients taking SSRIs have to be stable on their ongoing medications since at least 12 weeks.

The study procedures were carried out in accordance with the Declaration of Helsinki. The study was approved by our internal IRB and all participants had to sign the informed consent to be included in the study.

2.2.2. Assessment

To measure the severity of the hoarding symptoms, every participant was administered the UCLA Hoarding Severity Scale (UHSS) (Saxena et al., 2007b) immediately before and after the 12-week treatment period. The UHSS is a 10-item, clinician-administered scale that assesses the presence and severity of various components of the compulsive hoarding syndrome, including extent of clutter, urges to save items, excessive acquisition, difficulty discarding, social and occupational impairment, slowing, perfectionism, indecisiveness, and procrastination. Scores reflect the average occurrence of each symptom over the 1 week before and including the time of the interview. Its maximum score is 40. Every patient also completed the Saving Inventory-Revised
We also measure attention and impulsive symptoms through the Adult ADHD Self-Report Scale (ASRS) (Adler et al., WHO). The ASRS is an 18-item scale developed by the world health organization used both as a screening tool for adult ADHD and as a pre-post treatment assessment tool in ADHD trials. The scale quantifies patients about the DSM-IV symptoms with modifications to assess the adult presentation of ADHD psychopathology. The items are rated on a frequency basis: 0 = never, 1 = rarely, 2 = sometimes, 3 = often and 4 = very often. Nine symptoms refer to inattention and nine symptoms assess hyperactivity/impulsivity. For this study we used the Italian version of the ASRS and we measured both the total score and the subscores for inattention symptoms and impulsivity/hyperactivity symptoms (Gabriel and Violato, 2011).

2.2.4. Statistical analysis

Normality of variables was evaluated using Shapiro-Wilk W test. Repeated measures ANCOVA test was used to compare continuous or interval normally distributed pre-treatment and post-treatment clinical scales scores (UHSS, SI-R total score and subscales, ASRS total score and subscales, HAM-D, inverse HAM-A, GAF, SDS). The variable HAM-A was inverted (1/α) to make it normal. The effects of treatment were taken into account by introducing a dichotomous variable (presence/absence of drug therapy) into the ANCOVA model. Effect sizes were calculated using $\eta^2$ (partial eta squared) formula.

Pearson’s $r$ coefficient was calculated to evaluate the correlation of the difference of pre-treatment and post-treatment UHSS scores with atomoxetine dose, illness’ duration, baseline UHSS score and with the differences of pre-treatment and post-treatment of GAF, SDS and ASRS scales. Statistical tests were two-tailed. Level of significance was set at $p=0.05$. All analyses were performed on study completers and were carried out using STATA statistical software V.12.1 (StataCorp, Texas).

3. Results

3.1. Preclinical results

In Fig. 1 the effects of atomoxetine and fluoxetine on marble burying behaviour test in mice are compared. Atomoxetine (60 mg kg$^{-1}$ p.o.) and fluoxetine (30 mg kg$^{-1}$ i.p.) significantly reduced the number of buried marbles during the behavioural test in comparison to the control group treated with vehicle (Fig. 1a). The latency to the first marble buried was significantly increased in atomoxetine-treated mice and in fluoxetine-treated mice vs vehicle group (270.6 ± 17.2s, 270.0 ± 19.5 s and 168.0±9.5s, respectively) (Fig. 1b). Both treatments were able to rise the time spent in the corners (Fig. 1c) while did not change the number of rearings (Fig. 1d).

The integrity of motor coordination after the fluoxetine and atomoxetine administration was evaluated by the Rota rod test (Fig. 2a). No significant difference was observed in the number of falls at different times between vehicle- and atomoxetine-treated mice, while fluoxetine-treated rats showed a significantly increased number of falls in comparison to control animals (Fig. 2a). The effect of atomoxetine and fluoxetine on spontaneous mobility and exploratory activity was also evaluated in the Hole board test. Both parameters (holes, exploratory activity and board, mobility) were not altered in atomoxetine-treated group, whereas acute administration of fluoxetine reduced the exploratory activity of mice (Fig. 2b).

3.2. Clinical results

Twelve patients were enrolled in the study. Eleven out of 12 patients included completed the 12 weeks of atomoxetine treatment. One patient dropped out after the first week of treatment because of non-adherence to the treatment. Of the 11 completers 6 had at least one lifetime comorbid disorder, three had major depressive disorder (MDD), one obsessive-compulsive disorder (OCD) (without hoarding symptoms related to “typical” obsessions), one Tourette disorder and one binge eating disorder (BED). Baseline pre-treatment hoarding symptom severity was in the moderate to severe range, with a mean UHSS score of 28.91 and a mean SI-R score of 68.55. Nine out of 11 completers were under pharmacological treatment. Most of them were under medication for mild sleep disturbances (except for one patient taking risperidone for comorbid Tourette Disorder and a patient taking citalopram and mirtazapine for comorbid OCD) (for details see Table 3). Eight patients failed to respond to a previous serotonergic agent (two of them failed a previous treatment with venlafaxine and one of them failed to respond to a previous treatment with paroxetine). Moreover, two patients failed to respond to a previous trial of CBT with home visits.

The mean atomoxetine final dose of completers was 62.72 mg/day. Atomoxetine treatment was well tolerated and none of the patients report clinically significant changes of their hearth rate and blood pressure. One patient showed increased irritability after increasing atomoxetine dose from 40 to 80 mg; therefore, for this patient atomoxetine dose was tapered down to 40 mg until the end of the 12 weeks of treatment.

After 12 weeks of treatment the mean UHSS score decreased by 41.3% ($F(1.9) = 32.84, p = 0.0003$) for the whole group, and the mean SI-R score decreased by 39.9% ($F(1.9) = 27.24, p = 0.0006$) (see Table 2). The effect size for reduction in hoarding symptom severity with atomoxetine treatment was large ($\eta^2_p = 78.49$ for the
When we looked to different cluster of symptoms in the SI-R we observed a similar improvement in the three subscales (reduction of 41% ($F(1,9) = 18.64, p = 0.0019$) in clutter, 40.3% ($F(1,9) = 19.42, p = 0.0017$) in difficulty in discarding and 34.3% ($F(1,9) = 28.42, p = 0.0005$) in acquisition symptoms).

Six patients (54.5% of the total sample) were classified as full responders (defined as symptoms reduction greater than 35% and rating of at least 'much improved' on the CGI-I) and they showed a mean symptom reduction of 57.2%. Three patients (27.3% of the total sample) were classified as partial responders (defined as symptoms reduction in between 25% and 35%) and they showed a mean symptom reduction of 27.3%. Two patients (18.2% of the total sample) were classified as non-responders (defined as symptoms reduction less than 25%).

Inattentive and impulsivity symptoms showed a significant mean score reduction from baseline to the endpoint (18.5%) ($F(1,9) = 20.9, p = 0.0013$). Patients showed analogous improvements in inattentive (18.2%) and impulsive symptoms (18.7%) (see Table 2). Non-responders patients showed a 12.9% improvement while treatment-responders patients improved their score by 21.1%.

Global functioning score (measured through the GAF scale) increased by 29.1% at the endpoint ($F(1,9) = 27.5, p = 0.0005$) while disability score (measured through the SDS) decreased by 35% ($F(1,9) = 31.84, p = 0.0003$) (see Table 2).

The variable presence/absence of drug therapy never reached statistical significance in all the above tests.

UHSS score improvement showed a negative significant correlation with Atomoxetine dose, $r = -0.715$, $p = 0.013$. Atomoxetine mean dose of the 6 full responders was 55 mg while mean dose of the 3 partial responders was 67 mg. UHSS score improvement was not correlated with illness duration ($r = -0.367$, $p = 0.266$) and neither with UHSS pre-treatment score ($r = -0.038$, $p = 0.912$). There was no significant correlation between UHSS score improvement
Discussion

This is the first preclinical and clinical investigation assessing the effects of atomoxetine on the marble burying test in mice and on patients with a primary diagnosis of hoarding disorders. In our preclinical study atomoxetine significantly reduced the compulsive-like behaviours of mice in the marble burying test without affecting neither locomotor activity and coordination nor exploration behaviours. Indeed, atomoxetine reduced the number of marbles buried by mice, increases the latency to the first marble buried, the time spent in the corners and it shows a tendency to reduce the number of rears. When compared, atomoxetine and fluoxetine showed similar effects on the marble burying test. However, fluoxetine impaired locomotor activity in the rota rod test reducing motor coordination and it also decreased the exploratory activity in the hole board test. Thus, we cannot exclude that the reduction of marbles buried and the increase of the time spent in the corners induced by fluoxetine in the marble burying test may be related to motor function impairment.

The results of the clinical phase suggest that atomoxetine seems to be effective for the treatment of hoarding disorder, with a large effect size, and is well tolerated in these patients. Six patients were classified as full responders and three patients as partial responders at the end of the trial. The mean reduction of hoarding symptoms in the whole sample was quite large (41.3%) and full responder patients showed a mean symptoms reduction of 57.2%. Moreover, atomoxetine treatment was linked to an improvement of inattentive and impulsive symptoms. However, these effects on attention and impulsivity were not correlated to hoarding symptoms reduction. On the other hand, the atomoxetine effects on hoarding symptoms were correlated to a decrease of patient disability and to an improvement of their global functioning. Finally, atomoxetine worked at a relative low dose (mean of 62.72 mg).

Despite most of patients were under medications, also the two non-medicated patients showed a good response to atomoxetine and were both classified as partial responders. Moreover, except for a patient taking SRs all other patients were taking medications for mild sleep disturbances, suggesting that atomoxetine could be reasonable considered a potentially effective monotherapy for hoarding disorder.

Previous studies showed efficacy of the serotonergic drug paroxetine and the serotonergic/noradrenergic drug venlafaxine (Saxena et al., 2007a; Saxena and Summer, 2014). In these studies the mean symptoms reduction after 12 weeks of treatment was of 36% for the venlafaxine study and of 31% for the paroxetine study. In our study completers showed a higher mean symptoms’ reduction (41.3%) respect to the abovementioned studies and to previous CBT trials in which the mean symptoms reduction ranged from 10 to 28% (Tolin et al., 2015). Finally, atomoxetine showed greater effects on hoarding symptoms than that of methylphenidate in a previous small case series (Rodriguez et al., 2013). Moreover, in the present study atomoxetine was well tolerated while in the Rodriguez et al. study methylphenidate was discontinued because of intolerable side effects. However, the small sample size of our study does not allow us to conclude in favour of a clear superiority of atomoxetine versus these other interventions.

One of our initial hypotheses was that improving attention and reducing impulsivity would lead to a reduction of hoarding symptoms. Despite atomoxetine improved both hoarding and inattentive/impulsive symptoms we did not observe a significant correlation between these effects.

This observation seems to disprove the hypothesis that attentional and inhibitory control networks represent two core neurophenomenological dimensions of hoarding disorder. However, the lack of a proper neurocognitive assessment that enable us to detect more subtle changes in these networks, and the small sample does not allowed to drawn firm denial of this hypothesis. Thus any conclusion on this point should be better addressed in a larger
sample looking for clinical predictors and investigating attention networks and inhibitory control networks through a proper neuropsychological assessment.

Interestingly, in our sample 6 out of 8 patients who failed a previous trial with a serotonergic drug (two patients failed a previous venlafaxine treatment and one patients paroxetine) where classified as full responders (5 patients) or partial responders (1 patients). Thus, it seems that for patients who failed to respond to a serotonergic drug, atomoxetine could be a reasonable choice. Several interpretations are worth of mentioning for these results. Despite the neurobiology of hoarding disorder is mostly unknown, alerting attention networks and inhibitory control networks, in which noradrenergic pathways play a relevant role, seem to be critically involved in HD phenomenology. In this perspective our results are not completely in contradiction with the results of the venlafaxine study by Saxena and Summer (2014). In fact, in that study the final mean dose of venlafaxine was around 225 mg; at that dose venlafaxine showed substantial noradrenergic activity, while at dose lower than 150 mg it seems to have a prevalent norepinephrine transporter (NET) occupancy on both NET and SERT, with a higher occupancy on NET (Ding et al., 2014). Thus, we cannot rule out a possible serotonergic effect (Roseboom and Kalin, 2000). Of note, in agreement with this hypothesis, the two patients who failed a previous treatment with venlafaxine but responded to atomoxetine reported to have been treated with a maximum dose of venlafaxine of 150 mg (see Table 3). However, again, the small sample of our study does not permit to rule out other relevant hypotheses such as the existence of different biological subtypes or illness stages of hoarding patients responding to different kind of interventions. Several limitations are worth mentioning for both the preclinical and the clinical phase. The clinical phase is clearly limited by the open-label design and by the small sample size. Furthermore, the lack of a behavioural assessment of impulsivity (e.g. using a stop signal task) and attention (e.g. using a continuous performance test) limits the interpretation of the observed effects on attentive and impulsive symptoms measured by a self-rating scale as the ASRS. Moreover, the ASRS has not been validated for use in individuals without ADHD.

Concerning the preclinical phase, despite the marble burying test showed a good face and construct validity for compulsive disorders its main limitation is represented by its poor predictive validity (Albelda and Joel, 2012). Indeed, in order to differentiate its effect from a serotonergic medication such as fluoxetine, we measured several behaviors other than marble burying (rearings, time spent in the corner and latency to the first marble buried). However, we did not measure other putatively relevant behaviors such as digging, sniffing etc. Some studies suggested that medications that are able to reduce marble-burying behavior show a specific profile of actions on other behaviors assessed during the test (Hayashi et al., 2010). Moreover, we did not measure norepinephrine transporter (NET) and serotonin transporter (SERT) binding after ATX treatment. A recent study on monkeys showed that ATX, at clinically relevant dose, displays a dose-dependent occupancy on both NET and SERT, with a higher occupancy on NET (Ding et al., 2014). Thus, we cannot rule out a possible serotonergic effect of ATX on the observed changes in marble burying behaviour.

In conclusion, this preclinical and clinical investigations suggest

Table 2
Symptom rating scale scores before and after treatment.

<table>
<thead>
<tr>
<th>Scale</th>
<th>Pre-treatment score [mean (SD) or median (IQR)]</th>
<th>Post-treatment score [mean (SD) or median (IQR)]</th>
<th>ANCOVA test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[mean (SD) or median (IQR)]</td>
<td>[mean (SD) or median (IQR)]</td>
<td>F value</td>
</tr>
<tr>
<td></td>
<td>[mean (SD) or median (IQR)]</td>
<td>[mean (SD) or median (IQR)]</td>
<td>F value</td>
</tr>
<tr>
<td>UHSS</td>
<td>28.91 (SD 3.88)</td>
<td>17 (SD 7.28)</td>
<td>32.84</td>
</tr>
<tr>
<td>SI-R</td>
<td>68.55 (SD 9.22)</td>
<td>41.18 (SD 17.52)</td>
<td>27.24</td>
</tr>
<tr>
<td>ASRS</td>
<td>37.36 (SD 11.45)</td>
<td>30.36 (SD 9.71)</td>
<td>20.9</td>
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<td>ASRS-attention</td>
<td>21 (SD 6.08)</td>
<td>16.91 (SD 5.03)</td>
<td>15.05</td>
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<tr>
<td>ASRS-impulsivity</td>
<td>16.36 (SD 6.71)</td>
<td>13.45 (SD 5.73)</td>
<td>17.37</td>
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<td>DDS</td>
<td>23.45 (SD 2.98)</td>
<td>15.36 (SD 5.75)</td>
<td>31.84</td>
</tr>
<tr>
<td>GAF</td>
<td>55.27 (SD 5.85)</td>
<td>71.09 (SD 10.81)</td>
<td>27.5</td>
</tr>
<tr>
<td>HAM-D</td>
<td>4.54 (SD 1.75)</td>
<td>4 (SD 1.67)</td>
<td>0.7</td>
</tr>
<tr>
<td>HAM-A</td>
<td>3 (IQR 1)</td>
<td>4 (IQR 1.5)</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Table 3
Clinical and treatment variables of completer patients.

<table>
<thead>
<tr>
<th>Patient Lifetime comorbidity</th>
<th>Prior failed SRIs/ SNRS trials</th>
<th>Prior CRT with home visits trial</th>
<th>Ongoing medications</th>
<th>Maximum dose of atomoxetine</th>
<th>UHSS score reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Tourette Disorder</td>
<td>Citalopram (up to 60 mg)</td>
<td>–</td>
<td>Risperidone 1 mg since 2 years</td>
<td>50 mg</td>
<td>64, 28%</td>
</tr>
<tr>
<td>2 None</td>
<td>Vanlafaxine (up to 150 mg)</td>
<td>–</td>
<td>Lorazepam 2.5 mg since 4 weeks</td>
<td>40 mg</td>
<td>51,72%</td>
</tr>
<tr>
<td>3 None</td>
<td>Escitalopram (up to 20 mg)</td>
<td>–</td>
<td>None</td>
<td>40 mg</td>
<td>29,03%</td>
</tr>
<tr>
<td>4 Major Depressive Disorder</td>
<td>Vanlafaxine (up to 150 mg)</td>
<td>Yes (12 sessions)</td>
<td>Quetiapine 25 mg since 6 months</td>
<td>80 mg</td>
<td>35%</td>
</tr>
<tr>
<td>5 Binge Eating Disorder</td>
<td>Citalopram (up to 60 mg)</td>
<td>Yes (16 sessions)</td>
<td>Alprazolam 0.5 mg since 6 weeks</td>
<td>80 mg</td>
<td>25,90%</td>
</tr>
<tr>
<td>6 None</td>
<td>Citalopram (up to 40 mg)</td>
<td>–</td>
<td>Quetiapine 25 mg since 1 year</td>
<td>80 mg</td>
<td>23,30%</td>
</tr>
<tr>
<td>7 Major Depressive Disorder</td>
<td>Citalopram (up to 40 mg)</td>
<td>–</td>
<td>Clonazepam 1 mg since 8 months</td>
<td>80 mg</td>
<td>6,06%</td>
</tr>
<tr>
<td>8 None</td>
<td>Paroxetine (up to 40 mg)</td>
<td>–</td>
<td>Lorazepam 2.5 mg since 5 weeks</td>
<td>40 mg</td>
<td>64,28%</td>
</tr>
<tr>
<td>9 Obsessive-Compulsive Disorder</td>
<td>Citalopram 40 mg, mirtazapine 30 mg since 6 months</td>
<td>–</td>
<td>Lorazepam 2.5 mg since 5 weeks</td>
<td>40 mg</td>
<td>43,75%</td>
</tr>
<tr>
<td>10 Major Depressive Disorder</td>
<td>Sertraline (up to 200 mg)</td>
<td>–</td>
<td>Quetiapine 25 mg since 6 months</td>
<td>40 mg</td>
<td>52,94%</td>
</tr>
<tr>
<td>11 None</td>
<td>None</td>
<td>–</td>
<td>–</td>
<td>80 mg</td>
<td>25,92%</td>
</tr>
</tbody>
</table>
attention and inhibitory control are good targets for pharmacological intervention. Further controlled studies on larger sample are now needed.

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Contributors

Giacomo Grassi, Stefano Pallanti and Carla Ghelardini designed the study and wrote the protocol. Giacomo Grassi, Laura Micheli, Lorenzo Di Cesare Mannelli, Elisa Compagno, Carla Ghelardini and Stefano Pallanti managed the literature searches and analyses. Lorenzo Rigoli undertook the statistical analysis, and Giacomo Grassi wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

None of the authors have any competing financial interests in relation to this work.

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