THE ROLE OF ANTIDEPRESSANT TREATMENTS ON COGNITIVE DEFICITS A REVIEW OF RECENT LITERATURE

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Abstract

Objective: Nowadays, the interaction between cognition and emotions during a depressive disorder is an area of interest in the scientific literature. Patients with major depressive disorder (MDD) usually show alterations in various cognitive functions: attention, working memory, mental processing speed, executive functions.

Clinical observation of the effects of cognitive deficits on quality of life in patients with MDD, in euthymic and in relapse phases, needs a review of recent scientific literature on the impact of antidepressant treatment as a protective factor on the improvement of cognitive performances.

Method: Electronic PubMed and PsycInfo searches were conducted to identify research articles that focus on the effect of antidepressant treatments in responder and non-responder patients. We searched for papers published between 2006-2011, using the following keywords: major depressive disorder, cognition, neuropsychology and antidepressants. Our working group selected fifteen main scientific articles. These are: five non-blinded clinical trials, six case-control studies, three double-blind controlled clinical trials and a prospective part-randomised trial.

Results: Although some heterogeneous methodological aspects, the articles show comparable characteristics, such as common evaluation tools and point out that depression is characterized by specific biases in emotional processing that include negative information processing and deficits in cognitive control. An early antidepressants drug treatment (especially SSRIs and SNRIs) may play a protective role in cognitive impairment. SNRIs seem to have a stronger effect than SSRIs on cognitive functions, that persists even after cessation of treatment during recovery. We cannot establish if a neuroprotective function is attributable only to treatment or to the natural course of depression.

An appropriate drug treatment appears to be effective in improving cognitive abilities and depressive symptoms in elderly depressed patients. According to some authors, a bias in processing of appropriate stimuli varies with mood and individual history.

Conclusions: Although some conflicting data, impairment is frequently reported in the acute phases of the illness: depression is associated with impairment in everyday life functions and job performance. Traditionally, that impairment is seen as an effect of affective symptoms, but it was found that improvement of depression symptoms is not associated with a similar improvement on daily activities. A cognitive training could be useful in long-term anti-depressive treatment to prevent relapses and improve the quality of life.

In conclusion, cognitive functions and their importance in daily life should be taken into great consideration for their functional impact on patients and the psychiatrist's choices in terms of drug and rehabilitation treatment.

Key words: major depressive disorder, cognition, antidepressants, neuropsychology

Declaration of interest: none

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Introduction

According to literature, depression does not only change the way we feel emotions, but also the way we perceive ourselves and the world around us. Depression also affects the ability to think, concentrate, make decisions, formulate ideas, reflect and remember (Marazziti et al. 2010). Nowadays, the interaction between cognition and emotions during a depressive disorder is an area of interest in scientific literature.

Cognitive theories of depression suggest that people's thoughts, attitudes and interpretations and the way in which they attend to and recall information can increase their risk exposure to depression (Gotlib and Joormann 2010). Patients with major depressive disorder (MDD) show common alterations in various cognitive functions: attention, memory (especially working memory), mental processing speed, and executive functions (Reppemund et al. 2009). This data is confirmed by several studies (Ghormley et al. 2011, Iverson et al. 2011), some of which emphasize that the deflection of mood could be responsible for deficits in information processing, altered responses to negative feedback and making decisions. Some studies also

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emphasize that alterations in cognitive function may persist beyond the symptomatic phase of the disease (Fossati et al. 2002).

Neuropsychological studies of cognitive functions during depression identified quantitative abnormalities of the performance in many functional areas that would play a key role during the acute and the intercritical phases of the illness (Gorwood et al. 2008).

According to some authors, anti-depressant drugs could improve cognitive dysfunction in major depression (Clark et al. 2009). Drug treatments could play a protective role: the volume of the hippocampus is reduced in drug-free patients with chronic depressive illness, while the same changes were not found in treated subjects. The reduction in hippocampal volume is associated with impaired mnemonic of encoding informations (Sheline et al. 2003).

Objective

Inspired by the frequent clinical observation of the effects of cognitive deficits on the quality of life of patients with MDD, in both euthymic and relapse phases, we decided to revisit recent scientific literature about the impact of anti-depressant treatment on cognitive performances. This study arises from a clinical observation that needs confirmation from the scientific literature.

Methods

Criteria of article's selection

Electronic PubMed and PsycInfo searches were conducted to identify research articles that focus on the effect of antidepressant treatments in responder and non-responder patients. We searched for papers published between 2006-2011, using these keywords: major depressive disorder, cognition, neuropsychology and antidepressants. Our working group selected fifteen main scientific articles. These articles are: five non-blinded clinical trials, six case-control studies, three double-blind controlled clinical trials and a prospective part-randomised trial.

Papers were included by using the following criteria: English language, trials with adult patient samples (age ≥ 18) of N > 30, diagnosis of psychiatric disorder established according to DSM diagnostic criteria (American Psychiatric Association 1994), use of neuropsychological tests to estimate cognitive functions, use of Hamilton Depression Rating Scale (HDRS; Hamilton 1967) or Montgomery-Asberg Depression Rating Scale (MADRS; Montgomery & Asberg 1979) to assess affective disorders.

Methods and outcome measures in studies reviewed

These articles are: five non-blinded clinical trials (Mandelli et al. 2006, Gorlyn et al. 2008, Story et al. 2008, Herrera-Guzman et al. 2009, Li et al. 2010), six case-control studies (Galassi et al. 2006, Gualtieri et al. 2006, Thomas et al. 2009, Talarowska et al. 2010, Herrera-Guzman et al. 2010a, Herrera-Guzman et al. 2010b), three double-blind controlled clinical trials (Wise et al. 2007, Raskin et al. 2007, Culang et al. 2009) and a prospective part-randomised trial (Keers et al. 2010).

Using the specified criteria five reviews were also indentified (Castaneda et al. 2008, McLennan and Mathias 2009, Gotlib and Joormann 2010, Hasselbalch et al. 2010, Marazziti et al. 2010). These reviews were used to improve the analysis of the literature on the topic.

The first article (Mandelli et al. 2006) investigates the cognitive functions in patients with depressive symptomatic recovery, by comparing performances of responders and non-responders to the AD treatment. The sample was composed of 51 hospitalized patients (38 females and 13 males with mean age 52.3 $\pm$ 12.2) for a major depressive episode, according to DSM IV criteria. Exclusion criteria were: mental retardation (IQ<70), dementia, substance abuse/dependence, neurological disorder and severe organic disease. After a 7-day washout period, all patients were treated with fluvoxamine, to reach 300 mg daily from day 8 until the end of the trial, and evaluated at baseline and after 4 weeks using the 21-item HRDS. No concomitant drug was allowed except flurazepam and lithium maintenance. Cognitive functions were assessed with the WAIS-R (Wechsler 1997) once undertaken for all subjects: at the end of the fourth week of treatment.

The second article (Gorlyn et al. 2008) aims to characterize the cognitive profile associated with SSRI non response using neuropsychological tests. The sample consists of 32 adults meeting DSM IV criteria and SCID I (First et al. 1994) for current major depressive episodes. Two subjects are classified with bipolar disorder-currently depressed, three with bipolar disorder NOS-currently depressed, the remainder with major depressive disorder. Assessment followed two weeks (6 weeks for fluoxetine) of pre-treatment medication washout. All subjects received SSRI medication [paroxetine (10-60 mg QD), fluoxetine (40 mg QD), sertraline (50-200 mg QD), citalopram (20-40 mg QD), or escitalopram (10 mg QD)]. Only 15 subjects were treated exclusively with SSRIs. The remaining subjects received adjunctive anxiolytics, mood stabilizers, and non-SSRI antidepressants. No subjects were treated with antipsychotic medications or ECT in addiction to an SSRI. Clinical response was measured after 3-month open-label SSRI treatment. Treatment outcome was determinate by HDRS score. Responders were defined as having a decrease in HDRS score of at least 50% from baseline, plus a total follow-up HDRS score ≤ 10. Exclusion criteria are: neurological disease, acute medical conditions, illicit substance use. The domains and their composite tests were as follows: motor (Finger Tapping; Reitan and Davison 1974, Stroop Color Naming, Stroop Word Reading; Golden 1978), psychomotor (WAIS-III Digit Symbol, Trailmaking A and B; Reitan and Wolfson 1993), attention (Continuous Performance Task; Conners 2000, Stroop Color-Word), memory (Buschke Selective Reminding Test: Buschke and Fuld 1974), working memory (N-Back, A not B Reasoning Test), language (Letter and Category Fluency) and executive

(Wisconsin Card Sorting Test-number of categories; Heaton 1981, Trailmaking B-A) and general intelligence (WAIS-III Vocabulary subtest).

The third article (Story et al. 2008) examines neurocognitive variables (memory and executive functioning) that differentiated patients with late-life depression who showed robust versus weak responses to antidepressant therapy. The sample included 110 women and 67 men, with a mean age of 69.1 years (SD= 6.9) and mean education of 14 years (SD=3.3). Patients enrolled in the study met DSM IV criteria for MDD, completed both a structured diagnostic assessment for depression and neuropsychological testing at study entry and 1-year follow-up. One-hundred three patients were available for a follow-up assessment after 1 year. Clinicians rated patient depression using the Montgomery-Asberg Depression Rating Scale (MADRS). Subjects received pharmacological treatment for depression using the Somatic Treatment Algorithm for Geriatric Depression protocol (STAGED: Steffens et al. 2002). A small percentage of patients was not taking antidepressant because they were undergoing electroconvulsive therapy during the study. Exclusion criteria are: primary diagnosis of another major psychiatric illness, history of alcohol abuse, substance use problems, dementia and other factors or conditions that may affect neurocognitive performances. Neuropsychological assessments consisted of prose recall and percent retention (Wechsler Memory Scale III Logical Memory), word-list recall, attention and visuomotor processing speed (Trail Making A: Reitan 1955, Symbol Digit Modalities Test: Smith 1982), and mental flexibility (Trail Making B).

The fourth article (Herrera-Guzman et al. 2009) aims to compare the different efficacy profiles of SSRI versus SNRI treatments on improving the mnemonic and executive functions in drug naive patients with major depression. This clinical trial included 101 patients (32 men and 78 women) according to the following inclusion criteria: diagnostic confirmation with DSM-IV TR and the Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998), score of 18 points or higher in the HDRS-17, age between 20 and 50 years, antidepressant drug naive and drug-free of other psychopharmacological compounds. Exclusion criteria are: other major psychiatric diseases, history of substance abuse, use of oral contraceptives and major physical illness. Patients were also excluded if they showed an inefficient response to the pharmacological treatment after 4 weeks of initiation. From the 101 recruited patients, 73 completed the study and 28 abandoned it (treatment side effects, no compliance, inefficient response to treatment). Subjects were assessed by means of the HDRS-17 and a neuropsychological battery: CANTAB (Cambridge Neuropsychological Test Automated Battery; Robbinson et al. 1994), Wechsler Adult Intelligence Scale (WAIS-III) Vocabulary subtest to assess cognitive function in the premorbid period, the WAIS- III digit span for working memory, the Ray Auditory Verbal Learning Test (RAVLT; Schmidt 1996) and the battery Rivermed (RIVER) for verbal memory and learning, for visual-spatial memory and learning: pattern recognition memory (PRM Sahakian et al 1988), the Paired Associates Learning (PAL: Calkins 1894), the Delayed matching to sample (DMS) and the Spatial recognition memory (SRM) for the speed of information processing (evaluate both the mental and motor): The reaction time (RTI) and the Stroop test.

The fifth article (Li et al. 2010) evaluates the structural differences in gray matter volume by voxel-based morphometry (VBM) between patients able to achieve remission and those responding poorly to antidepressants. The sample consists of 48 adults (from 21 to 65 years) met DSM-IV criteria for MDD. After screening subjects received open-label antidepressant treatment (SSRI, SNRI or buproprion) for the next 6 weeks. Exclusion criteria are: alcohol or substance abuse history, major physical or neurological illness, other major psychiatric diseases. Individual assessments of pre and post-treatment mood included ratings with the HDRS-17 and Young Mania Rating Scale (YMRS: Young 1979). After antidepressant treatment, subjects were assessed by neurocognitive tests: Tests for Attentional Performance, Word Lists Test for verbal memory function and the Face Test for visual memory function, The Wisconsin card sorting test (WCST) to evaluate executive functions during the time between the immediate word/face recall test and the delayed word face recall test. Imaging studies consist of: Magnetic resonance imaging (MRI) and an optimized VBM protocol.

The sixth article (Galassi et al. 2006) investigates memory in major depressed patients in adult-senile age before and after remission of depression, comparing them with normal volunteer controls. In addition, this study compares the antidepressant efficacy of fluoxetine and reboxetine at baseline and six months later to determine if agents with selective serotonin or norepinephrine reuptake have different effects on cognitive functions in depressed patients. The sample consists of 48 drug-free patients (aged over 50 years) meeting DSM-IV criteria for MDD (single episode or recurrent) and a control group of 15 healthy volunteer controls matched for age and education level. Exclusion criteria are: global mental deterioration or neurological and internal disease, a lifetime diagnosis of schizophrenia or recent history of alcohol/substance abuse. All patients had been psychotropic medication-free for at least 6 weeks before recruitment (only a low dosage of benzodiazepines assumed continuously for a long time was admitted). The 48 patients were randomly assigned to treatment with fluoxetine or reboxetine, the neuropsychological investigator being blind to the treatment. Both the value of HRDS and the clinical evaluation were adopted to define full remission. The following assessment tools were used: HRDS and Geriatric Depression Scale (GDS; Yesavage et al. 1983) to evaluate depression; Mini Mental State Examination (MMSE) to evaluate the mental deterioration; Wechsler Memory Scale (WMS), Attentional matrices (Spinnler & Rognoni 1987), Familial face recognition, Famous faces recognition (Faglioni et al. 1991), Stem completion test (Graf et al. 1984), Autobiographical memory (Borrini et al. 1989), MLT'88 (Andreani et al. 1990): test for historical events to explore attention, implicit memory, anterograde and retrograde memory (autobiographic and for public events).

The seventh article (Gualtieri et al. 2006) is a

retrospective cross-sectional study of neurocognitive performance in patients with depression and healthy subjects. The aim of this study is to evaluate the impact of neurocognition on diagnosis, subtypes and treatment (especially cognitive-based therapies) in depression. The group of cases (69 subjects) was divided into two subgroups: drug-free patients and antidepressant monotherapy responders. They were compared to 69 healthy subjects.

The subjects of this investigation were unipolar, non psychotic patients with major depressive disorder. Patients'psychiatric diagnoses were conferred by using DSM-IV-TR criteria. No comorbid diagnoses were permitted. Subjects were assessed by means of the HDRS-17 and a neuropsychological battery. Patients' neurocognitive performance was measured on a computerized battery of tests, CNS Vital Signs. CNS Vital Signs is a PC-based neurocognitive screening battery, comprising of seven familiar neuropsychological tests: verbal and visual memory (verbal memory, visual memory), finger tapping test, symbol-digit coding, Stroop test, shifting attention test and continuous performance test.

The eighth (Thomas et al. 2009) is a case-control study (75 cases and 82 controls) designed to evaluate the different profiles related to cognitive performance in depressed patients a young age as compared to depressed older patients. Both groups of cases and controls were divided into two subgroups based on age. Authors compared the psychological performances of the two subgroups of cases each other and with healthy controls by assessing four neurocognitive domains: attentional and executive functions, verbal memory and working memory and speed of information processing. The subjects were screened by using: neuro-psychiatric assessment, physical examination, assessment haematochemical and cognitive screening with MMSE. Severity of depression was assessed by using the MADRS. The neuropsychological aspects were assessed by: NART (National Adult Reading Test: Nelson 1982) the IQ premorbid, CANTAB in the different subtests: Controlled Oral Word Association Test (Benton's FAS, Benton et al 1983), Spatial Working Memory (CANTAB), Vigil Continuous Performance Test (CPT Vigil; Cegalis 1991), Rey Auditory Verbal Learning Test (RAVLT), Pattern recognition (CANTAB), Spatial recognition (CANTAB).

The ninth article (Talarowska et al. 2010) is a case-control study designed to evaluate whether antidepressive therapy improved the efficiency of cognitive processes among patients suffering from depression disorder and determine possible associations between auditory-verbal declarative and working memory performance, evaluated before treatment versus remission degree after treatment. The study was carried out in a group of 87 subjects (men=32) aged 20-62 (M 40.14 years, SD 12.37 years). The participants were divided into 2 groups: patients with depressive disorder (n=30) and healthy subjects (n=57). Qualification of depressive patients into the study group was based on the diagnostic criteria according to ICD-10. The severity of depression was assessed by the 21-item HDRS. Patients were examined during hospitalisation. The presence of axis I and II disorders (other than depressive episode) and some diagnosis of somatic diseases and injuries of the central nervous system were regarded as exclusion criteria. Both in patients and control group history was obtained using the standardized Composite International Diagnostic Interview–CIDI (Robins et al. 1989). Patients were treated with SSRIs. Regarding the patients with depression disorder, HDRS, the Stroop Test and AVLT were applied at the therapy onset and after 8 weeks of the therapy continuation. In the comparison group the Stroop Test and AVLT were performed in single examination.

The tenth (Herrera-Guzman et al. 2010a) evaluates the effects of SSRIs and SNRIs on working memory, attention and cognitive functions in patients with MDD. It is a case-control study in which the group of 73 subjects with MDD in the previous study (Herrera-Guzman et al. 2009), treated with escitalopram 10 mg / day (n = 36) or duloxetine 60 mg / day (n = 37) was compared with a group of 37 controls by the administration, in two times at 24 weeks of each other, of HAM-D-17 and a neuropsychological battery. Patients and controls were divided into three groups based on age, years of schooling and WAIS III vocabulary score. The following assessment tools were used: Cambridge Neuropsychological Test Automated Battery (CANTAB), WAIS III vocabulary subtest (to assess premorbid intellectual functioning); WAIS III Digit span (to assess attention and working memory), Spatial Working Memory (SWM), Rapid Visual Information Processing (RVIP) to assess sustained attention; Match to Sample Visual Search (MTS) to assess selective attention and speed of processing information; Stroop test to assess the psychomotor speed and inhibition of automatic responses; September Intra-Extra-Dimensional Shift (ID/ED) to assess attentional persistence; Stockings of Cambridge (SOC) to assess the skills of planning.

The eleventh study (Herrera-Guzman et al. 2010b) consists of a 24-week follow-up on patients and controls included in the previous clinical trial (Herrera-Guzman et al. 2010a) to evaluate the possible effects of SSRIs and SNRIs on cognitive function in drug-naive patients with major depression; they were assessed after complete recovery. They observed a drop-out in the sample of patients treated with duloxetine. The following assessment tools were used: CANTAB, WAIS III vocabulary subtest (to assess premorbid intellectual functioning), Spatial Working Memory (SWM) (to assess working memory), Rey Auditory Verbal Learning Test (RAVLT) (to assess verbal learning and memory), Visual learning and memory, Paired Associates Learning (PAL) to assess learning and visual memory, Rapid Visual Information Processing (RVIP) to assess attention, Stockings of Cambridge (SOC) for the planning of executive functions. The subjects were tested at the end of the clinical trial and after 24 weeks of treatment discontinuation, the controls were also texted twice: at T0 and after 24 weeks.

The twelveth study (Wise et al. 2007) aims to evaluate the efficacy and tolerability of anti-depressant treatment with duloxetine in elderly patients with internistic comorbidity. This is a randomized, double-dummy clinical trial conducted on two samples, which have been both treated at first with placebo for one week, and then randomized to 8 weeks of treatment with duloxetine 60 mg / day (n= 207 subjects) and a

placebo (104 subjects) respectively. Both groups include patients older than 65 years, fulfilling the DSM IV-TR criteria for MDD and undergo diagnostic confirmation through the use of the MINI, HAMD and MMSE. Among the exclusion criteria: other axis I diagnoses in the DSM IV-TR, cognitive impairment, mental retardation and serious organic disease. Medical comorbidities that affect the patients include: vascular disease (cardiovascular and cerebrovascular diseases), diabetes mellitus, and arthritis, as assessed by previous clinical examination and diagnosis. The assessment tools, in order to evaluate the cognitive function, were the Verbal Learning and Recall Test (VLRT), the Digit Symbol Substitution Test (SDST), 2-Digit Cancellation test (2DCT), and the Letter Sequencing Numbr-test (LNST). These tests were chosen in order to explore the verbal memory and learning, attention, executive functions and working memory. Other measures used for what concerns the emotional profile were: GDS, HDRS, the Visual Analogue Scale (VAS) for pain, CGI-S (Guy 1976) and the Short Form Health Survey (Ware et al 1992).

The thirteenth study (Raskin et al. 2007) is another controlled, randomized double-blind, clinical trial, that assesses the effectiveness of duloxetine versus placebo in improving cognitive performance in elderly depressed patients with chronic pain. The same sample described in the previous trial was analyzed, using the same rating scales. The following biological parameters were used as measures of safety and tolerability: weight, blood pressure supine and standing positions, heart rate, ECG, urinalysis and blood tests.

The fourteenth study (Culang et al. 2009) is a randomized double-blind placebo-controlled trial examining the impact of citalopram on cognitive functioning in late-life depression. The sample consists of 174 community-dwelling men and women aged 75 years and older meeting DSM IV criteria for nonpsychotic unipolar depression (single or recurrent) with a baseline HRDS score e”20. The duration of this study was 8 weeks. All patients began the trial with a 1-week single-blind placebo lead-in with the baseline visit conducted at the end of the lead-in. Patients were randomized to citalopram 20 mg/day or matched placebo only if they continued to meet inclusion criteria at the end of placebo lead-in. Neuropsychological assessments included mental status (MMSE), psychomotor speed (Wechsler Adult Intelligent Scale-III Digit Symbol Subtest), reaction time (Choice Reaction Time; Thorne et al. 1998), visual-spatial skill (Judgment of Line Orientation; Benton et al. 1983), executive functioning (Stroop Color/Word Test), and memory (Buschke Selective Reminding Test; Buschke 1974).

The fifteen study (Keers et al 2010) aims to study the association between stressful life events (SLEs) occurring in the six months prior to treatment, with the severity of symptoms at baseline and investigate the effects of SLEs on change in cognitive symptoms of depression during the antidepressant treatment. The sample was made of 728 participants by using GENDEP: a prospective part-randomised pharmacogenomics trial which collects longitudinal data on the symptoms of patients with major depression treated with a selective serotonin reuptake inhibitor (escitalopram) or a tricyclic antidepressant (nortriptyline). Participants aged between 18 and 75 and were recruited from nine treatment centers in eight European countries, they were randomized to receive nortriptyline or escitalopram. Depression severity was measured at the baseline and weekly over the 12 week trial, using the MADRS, the HDRS and the Beck Depression Inventory (Beck AT 1967). The List of Threatening Experiences Questionnaire (Brugha et al 1985) was used, at the baseline, to measure the occurrence of SLEs that patients had experienced in the six months prior to treatment.

The main features described in the selected articles are summarized in **table 1**.

Results

Mandelli’s study (Mandelli et al. 2006) investigates the impact of symptom remission during treatment on cognitive functioning. Patients were divided in two groups: responders (n=34) and non- responders (n=17), according to the decrease in HDRS scores to 7 or less. The first group (responders) showed higher total scores at the WAIS-R than non-responders. Responders had approximately 10 points higher Verbal, Performance and Total IQ scores and a lower incidence of Cognitive impairment. Two great limitations of this study were the lack of a premorbid IQ assessment and the inclusion of both major depressives and bipolar patients, in fact inclusion criteria was patients affected by Mood Disorders with a major depressive episode.

Gorlyn’s group (Gorlyn et al. 2008) shows that SSRI responders outperformed nonresponders across all cognitive domains, with the largest difference observed in executive, language (Letter Fluency but not Category Fluency) and working memory functions, though the groups did not differ in Vocabulary score, an estimate of general intellectual functioning. Their results indicate poorer global cognitive functioning is predictive of treatment nonresponse. Deficits are most pronounced in tests demanding greater mental search and manipulation rather than speeded motor output. Cognitive slowing may mediate the working memory and executive function deficits found in nonresponders. This study is limited by its small sample size, inclusion of both major depressives and bipolar patients and use of adjunctive pharmacological treatment (mood-stabilizers, anxiolytics and non-SSRI antidepressants).

Story’s study (Story et al. 2000) points out that depressed older adults with poor baseline performances on tests of verbal memory and processing speed demonstrated less treatment response over 1 year than patients with better cognitive test results. These differences remained after controlling for depression severity at both time-points. Severity of depression at baseline did not seem to influence the relationship between baseline neurocognitive function and the magnitude of treatment response. This study did not include a control group.

Herrera-Guzman’s study (Herrera-Guzman et al. 2009) shows that both the treatment with SSRIs and with SNRIs induce an improvement of the cognitive functions in patients with MDD. In fact episodic, verbal

and spatial memory are the most involved functions, while working memory and speed of information processing are the least improved. SNRIs probably induce more stable improvements than SSRIs.

Li's study (Li et al. 2010) points out that there were significant structural differences between remitting and non-remitting patients after antidepressant treatment. Many of the structural abnormalities were correlated with the severity of depression and cognitive dysfunction. Patients with remission had minimal attention problems with reduced gray matter volume (GMV) over left postcentral parietal gyrus (BA 3) and bilateral superior/medial frontal gyrus (BA 6). In contrast, the non-remitting patients showed more cognitive problems including poor acoustic and visual attention, and they also presented a significant GMV reduction in the left dorsolateral prefrontal cortex (DLPFC-BA 9) when compared with the other two groups. This VBM study indicates that patients with MDD are heterogeneous, and not all MDD patients have the same morphological deficits. Furthermore, it implies that severity of depression and patients' responses to antidepressants should also be taken into consideration when investigating structural alterations in MDD. The interpretation of these results needs to be tempered by five limitations: gender differences may influence GMV deficits in depression; patients recruited were not drug-free but all were treated with antidepressants; comorbid psychiatric conditions in the depressives did not take into consideration; patients recruited were all recurrent MDD patients; all patients were Chinese and the results might not be generalized to MDD patients worldwide.

Forty-two patients enrolled completed the Galassi's study (Galassi et al. 2006). At T0, the entire group of patients had worse performances than controls in MMSE, in a few subtest (information, logical memory and paired associated learning) and total score of Wechsler Memory Scale and in autobiographical memory. No differences were detected in attention task (Attentional Matrices), implicit memory (Stem test), face recognition and memory for historical events (MLT test). Remitters at T0 had the same impaired tasks and at T6 had significantly improved in MMSE, Wechsler Memory Scale total score and many memory tests but they still differed from volunteer controls in a few complex tasks requiring more cognitive effort. There were not differences between fluoxetine and reboxetine. The limitations of this study are: the small sample and only attention and memory were investigated.

Gualtieri's group (Gualtieri et al. 2006) shows that patients with depression are subject to multiple neuropsychological deficits. According to their results patients treated with modern antidepressants are better cognitively than untreated ones, but they do not perform better than healthy subjects. The most important differences concern cognitive flexibility complex attention, processing speed and vigilance attention. This study shows that deficits in some domains may be more important than others. Analyses indicate differences between untreated major depressive disorder patients and healthy subjects in measure of cognitive flexibility, processing speed and vigilance attention. Treated patients performed better than untreated patient in cognitive flexibility, processing speed and complex attention. These data could demonstrate that these two measures of executive ability are central to the neurocognition of depression and that deficits in these areas are responsive to successful treatment. The limitation of this study consists on the use of a computerized battery which could be associated with nervousness during testing and with poor results in certain tasks.

In the Thomas' study (Thomas et al. 2009) statistical analysis show no significant differences in the scores of MMSE, NART (National Adult Reading Test), or in the years of schooling among the younger and the older subjects. There were no differences in the severity (MADRS) between the two subgroups of patients. Evaluating the four neurocognitive domains (after excluding patients treated with anticholinergics), differences between the 2 groups were observed in verbal memory and neurocognitive impairment. In this comparison on neurocognitive performance of older and younger subjects with MDD a significant difference in learning and verbal memory was found as well as a slight difference in speed of processing information in the group of older subjects. The neurocognitive impairment is, therefore, significantly altered in older depressed subjects. Those who had a later onset show more depressive deficits than subjects with an earlier age of onset. Differences in visuospatial learning, attention and executive functions were not identified between the groups. The neurocognitive impairment, according to the results obtained in young and elderly depressed patients, actually seems to be related to the disease itself. In particular, higher cognitive deficits were observed in late-onset depression. The limitation of this study is the small sample.

In the study of Talarowka (Talarowka et al. 2010) the results indicate that depressive disorders are associated with failure to delete irrelevant information from the working memory, with simultaneously impaired executive functions and auditory-verbal declarative memory (short term and long term) in comparison with healthy subjects. After a period of 8-week pharmacotherapy patients showed better outcomes in the Stroop Test part B (errors). There were not any significant differences in the performance levels of the Stroop Test and AVALT in remitted patients versus non-remitted. There was not improvement in the efficiency of auditory-verbal, declarative or working memory after 8-week therapy. The obtained results may indicate the failure of administered medical agents to improve the cognitive functionality in the studied patients. The limitation of this study is the small sample.

Herrera-Guzman's study (Herrera-Guzman et al. 2010a), focusing on the same sample of previous study (Herrera-Guzman et al. 2009), shows that depressed subjects report changes in the areas of attention and cognition (working memory, sustained attention, inhibition of automatic responses, set-shifting schedule) which improved after the administration of SSRIs and SNRIs. These improvements, however, will not reach the performance levels of the controls, and suggest that the recovery of the cognitive functions is incomplete in patients in remission. A limitation of the study is that cases and controls are not matched by gender.

The following article of Herrera-Guzman (Herrera-Guzman et al. 2010b) shows that the two groups of patients undergoing treatment for depression have

Table 1

Study	Drugs	Follow-up	Evaluations	Outcomes
Mandelli et al. 2006	Fluvoxamine (n=51)	4 weeks	HDRS-17, WAIS-R	Improvement in responders at the WAIS-R
Gorlyn et al. 2008	Paroxetine (n=21), Fluoxetine (n=1), Sertraline (n=4), Citalopram (n=4), Escitalopram (n=2)	12 weeks	SCID-I, HDRS-17, Finger Tapping, Stroop test (color naming, word reading, color-word), WAIS-III (digit symbol, vocabolary subtest), TMT A and B, CPT, SRT, N-Back, A not B Reasoning Test, Letter and Category Fluency, WCST (number of categories)	Improvement in SSRI responders in executive, language and working memory functions
Story et al. 2008	not specified (n=177)	one year	MARDS, TMT A and B, SDMT, WMS-R (LM)	Less treatment response in depressed older adults with poor baseline performances
Herrera-Guzman et al. 2009	Escitalopram (n=36), Duloxetina (n=37)	24 weeks	HDRS-17, CANTAB, WAIS III (vocabulary subtest, digit span), SWM, RAVLT, RIVER, PRM, PAL, DMS, SRM, RTI, Stroop test	No differences in the improvement of cognitive functions in patients treated with SSRIs or SNRIs
Li et al. 2010	SSRI, SNRI, Bupropion (n=48)	6 weeks	HDRS-17, YMRS, Tests for Attentional Performance, Word Lists Test, Face Test, WCST	Structural differences between remitting and non-remitting patients
Galassi et al. 2006	Fluoxetine (n=24), Reboxetine (n=24); healthy subjects (n=15)	six months	HDRS, GDS, MMSE, WMS, Attentional matrices, Familial faces recognition, Famous faces recognition, Stem completion test, Autobiographical memory, MLT'88	No differences in the improvement of cognitive functions in patients treated with fluoxetine or reboxetine
Gualtieri et al. 2006	not specified (n=31), drug-free (n=38); healthy subjects (n=69)		HDRS, CNS Vital Signs, Symbol-digit coding, Stroop test, Shifting attention test, CPT	Better performances in processing speed and complex attention in patients treated with antidepressants but worse than healthy subjects
Thomas et al. 2009	Fluoxetine (n=16), Sertraline (n=4), Citalopram (n=6), Paroxetine n=4); healthy subjects(n= 57)		NART, CANTAB, Vigil CPT, RAVLT	Higher cognitive deficits were observed in late-onset depression

Table 1 *(continued)*

Talarowska et al. 2010	Fluoxetine (n=16), Sertraline (n=4), Citalopram (n=6), Paroxetine (n=4); healthy subjects (n=57)	8 weeks	HDRS, Stroop Test , AVLT, CIDI interview	No significant differences in cognitive performances in remitted patients versus non-remitted
Herrera-Guzman et al. 2010a	Escitalopram (n=36), Duloxetina (n=37); healty subjects (n=37)	24 weeks	HDRS-17, CANTAB, WAIS III (vocabulary subtest, digit span), SWM, RVIP, MTS, Stroop test, ID/ED, SOC	Better performances in processsing speed and complex attention in patients treated with both SSRIs and SNRIs but worse than healthy subjects
Herrera-Guzman et al. 2010b	Escitalopram (n=36), Duloxetina (n=36); healthy subjects (n=37)	24 weeks	CANTAB, WAIS III (vocabulary subtest), SWM, Working memory, RAVLT, Visual learning and memory, PAL, RVIP, SOC	SNRIs seem to have better effects on memory than SSRIs
Wise et al. 2007	Duloxetine (n=207), Placebo (n=104)	8 weeks	VLRT, SDST, 2DCT, LNST, GDS, HDRS, VAS, CGI-S, SF-36	A better response in cognitive domains among patients with comorbid organic treated with duloxetine versus placebo
Raskin et al. 2007	Duloxetine (n=207), Placebo (n=104)	8 weeks	VLRT, SDST, 2DCT, LNST, GDS, HDRS, VAS, CGI-S, SF-36	Improvement in cognitive performances in patients with chronic pain treated with duloxetine versus placebo but no significant difference in improving total MMSE scores
Culang et al. 2009	Citalopram (n=84), Placebo (n=90)	8 weeks	HDRS, MMSE, CRT, JOLO, Stroop test (color/word), WAIS-III (digit symbol subtest,) SRT	A possible deleterious effect of citalopram on cognition among non-responder patients aged 75
Keers et al. 2010	Escitalopram or Nortriptyline (n=728)	12 weeks	MADRS, HDRS-17, BDI, LTE-Q	SLEs occuring prior to treatment may predict response to antidepressants

Legenda: AVLT (Auditory-Verbal Learning Test by Luria); BDI (Beck Depression Inventory); CANTAB (Cambridge Neuropsychological Test Automated Battery); CGI-S (Clinical Global Impression-Severity); CIDI (Composite International Diagnostic Interview); CPT (Continuous Performance Task); CRT (Choice Reaction Time); 2DCT (2-Digit Cancellation test); DMS (Delayed matching to sample); GDS (Geriatric Depression Scale); HDRS (Hamilton Depression Rating Scale); ID/ED (Intra-Extra-Dimensional Set Shift); JOLO (Judgment of Line Orientation); LNST (Letter-Number Sequencing test); LTE-Q (List of Threatening Experiences Questionnaire); MADRS (Montgomery-Asberg Depression Rating Scale); MMSE (Mini Mental State Examination); MTS; (Match to Sample Visual Search); NART (National Adult Reading Test); PAL (Paired associates learning); PRM (Pattern recognition memory); RAVLT(Ray auditory verbal learning test); RIVER (Rivermed battery); RTI (Reaction Time); RVIP (Rapid Visual Information Processing); SCID I - II (Structured Clinical Interview for DSM); SDMT (Symbol Digit Modalities Test); SDST (Symbol Digit Substitution test); SF-36 (Short Form Health Survey); SOC (Stockings of Cambridge); SRM (Spatial recognition memory); SRT (Buschke Selective Reminding Test); SWM (Spatial Working Memory); TMT-A (Trail Making Test Part A); TMT-B (Trail Making Test Part B); VAS (Visual Analogue Scale); VLRT (Verbal Learning and Recall test); YMRS (Young Mania Rating Scale); WAIS-R (Wechsler Adult Intelligence Scale); WMS-R (Wechsler Memory Scale-Revised): LM (Logical Memory subtest); WCST (Wisconsin Card Sorting Test)

overlapping WAIS scores. The control group has slightly higher values, although this difference is not statistically significant. The patients in remission who have cognitive dysfunctions also show deficits in verbal and visual episodic memory, sustained attention, strategic aspects of working memory and planning. Patients show the same pattern of neuropsychological deficits after a period of 24 weeks without treatment. This suggests that cognitive dysfunctions persist beyond clinical symptoms. The patients previously treated with SNRIs show better performance in visual and verbal episodic memory, compared to those previously treated with SSRIs. This study confirms the presence of cognitive impairment in treated patients. Besides, the authors observed that patients had a recovery for clinical symptoms, but not for neuropsychological capacities. So cognitive deficits can persist in asymptomatic patients and in patients no longer treated with medications and that have been in recovery for several months. However, it seems that SNRIs can have better effects on memory than SSRIs. Cognitive impairment appears to be the stable dimension in depressed patients both in remission and in recovery and previously treated with SSRIs and SNRIs. This work suggests a possible upgrading of SNRIs on visual and verbal memory.

In the study by Wise (Wise et al. 2010) it was possible to observe a greater increase in the scores of cognitive functions among patients with comorbid organic and treated with duloxetine versus patients treated with placebo. On the contrary no significant difference was found in the improvement of cognitive performance in the subjects with no medical comorbidity and treated with SNRI versus placebo. A greater benefit of the treatment with SNRIs has been detected by an increase of SF-36 scores and in particular patients with cardiovascular disease are more likely to respond to SNRIs (with a significant difference in improvement versus depressed patients without vascular disease). It was also noted that the state of medical comorbidity did not interfere with the effectiveness of the treatment with duloxetine in the response and remission of symptoms.

The following study by Raskin (Raskin et al. 2007) analyzes the previous sample, but also assesses the impact of treatment with duloxetine versus placebo in the improving of cognitive performance in patients with chronic pain, showed increased scores. These scores were higher for patients treated with duloxetine versus placebo in the GDSc after the first week of treatment and in the subsequent weeks, while an improvement of the scores in the CGI-S and the HRSD has been respectively obtained from the second and fourth week of treatment, with major differences in patients with severe depression. The highest increases of the scores were observed in the Verbal Learning and Recall Test and in the verbal learning and memory, with no significant difference in patients treated with duloxetine versus placebo in improving the total MMSE scores. Rates of remission and recovery were higher in patients treated with SNRIs. In the matter of the scales measuring algic symptoms, a significant difference was found in patients treated with doluxetina using the Visual Analogue Scale for back pain. No significant difference compared to placebo was found in the improvement of algic symptoms (such as headache and neck pain), and in the interference of pain on daily activities.

Culang's group (Culang et al. 2009) points out that citalopram nonrespoders were the only group of the study to decline on verbal learning and psychomotor speed. Citalopram responders showed significant improvement in visuospatial functioning, when compared with non responders in either condition, but their improvement was not greater than responders on placebo. The authors suggest that medication may have a deleterious effect on some aspects of cognition among patients aged 75 years and older who have not responded and that patients should not be maintained on a medication if they have not had an adequate response. This study should be interpreted in the context of several limitations: there were statistically significant differences between the two treatment conditions and the four patient groups at baseline on several NP tests; it may be possible that including a small number patients with MMSE=24 in this study might have influenced their results; there were missing data; a somewhat limited NP battery was used.

In the study of Keers (Keers et al. 2010) no correlation was founded between the occurrence or the number of SLEs and the baseline MADRS and HDRS scores; while both the occurrence and increasing number of SLEs were associated with higher BDI scores. Both the occurrence and the increasing number of SLEs reported predicted greater improvements in cognitive symptoms in patients treated with escitalopram, while neither the occurrence nor the number of SLEs reported had an effect on the cognitive symptoms of patients treated with nortriptyline. The occurrence and the increasing number of SLEs were associated with higher baseline cognitive symptoms, patients who reported stress showed a greater improvement in cognitive but not neurovegetative or mood symptoms during treatment and the association between SLEs and improvements in cognitive symptoms was specific to patients treated with escitalopram. The results could suggest that SLEs occurring prior to treatment may predict response to antidepressants, moreover, the occurrence of SLEs is associated with a depressive episode where cognitive symptoms dominate the clinical picture and these symptoms result in a more improved response to escitalopram, suggesting that higher cognitive symptoms may benefit more from treatment with SSRIs than TCAs. Some limitations are: the collected data on SLEs occurring 6 months prior to current depressive episode and do not include the severity of SLEs and some of the reported SLEs are unrelated to the pathophysiology of the depressive episode; the LTE-Q is a retrospective self-report measure of the SLEs and is subject to a number of biases especially in the context of depressive illness.

Discussion and conclusions

The literature seems to confirm the data obtained from longitudinal studies on higher cognitive disfunctions in patients with MDD, according to which the clinical history of these patients shows persistent neuropsychological deficits (Martinez-Aran et al. 2997;

Clark et al. 2009).

Among the studies reviewed, the research carried out by the group of Herrera-Guzman (Herrera-Guzman et al. 2009) highlighted that an adequate and early pharmacological treatment with AD as SSRIs and SNRIs, may play a protective role against cognitive impairment, especially the visual and verbal memory. This effect, higher for the SNRIs, seems to persist even after the cessation of the treatment, during recovery (Herrera-Guzman et al. 2010b). Nevertheless there is no such evidence between the two treatment (Herrera-Guzman et al. 2010a) in study carried out in the same year on patients with depressive symptomatology. A possible explanation could be that serotonergic and noradrenergic action of SNRIs determinate neuroplastic effects on hippocampal formation, helping to improve the mnemonic capacity and this effect could be maintained and strengthened in the long term, as the gradual effect of antidepressant treatment (Sheline et al. 2003).

Further confirmations about the improvement of the neurocognitive profiles in patients treated with SNRIs derives from the studies of Wise (Wise et al. 2010) and Raskin (Raskin et al. 2007): in the first one, patients with medical comorbidity and treated with duloxetine showed increased cognitive abilities, a reduction of the HDRS and SF-36 scores. The second study reported similar results in patients with chronic pain. Even within the category of elderly depressed, therefore, an appropriate drug treatment appears to be effective in improving both cognitive capacities that general depressive symptoms. Duloxetine, in particular, proved effectiveness also in patients with organic comorbidity.

According to the actual findings in the literature, we can not establish whether a neuroprotective function is attributable to the treatment (that can lead to an improvement of cognitive performance in depressed patients) or rather to a favorable course of the disorder.

The role of antidepressant drugs on these cognitive functions may be partly explained by recent research that suggest their involvement on neuronal plasticity and connectivity. Escitalopram is likely to activate the TrkB brain-derived neurotrophic factor in the anterior cingulate cortex (Rantamäki et al. 2007), duloxetine is likely to induce the up-regulation of brain-derived neurotrophic factor mRNA in the prefrontal cortex of rodents (Calabrese et al. 2007). Recent studies have also found that some genes may be implicated in depression and in the changes of specific cognitive functions. In particular, the gene for the serotonin transporter seems to be implicated in the genesis of depression (Uher et al. 2010; Risch et al. 2009). Further studies are trying to examine an association between the serotonin transporter and the cognitive biases of depression.

But these results are not confirmed by the study of Talarowka (Talarowka et al. 2010) that shows the failure of administered antidepressant drugs to improve the cognitive functionality. An interesting thought about this could result from the Li's study which shows differences in brain of responder and nonresponder patients; differences that may be related to the severity of the clinical and cognitive dysfunction.

A review of Marazziti (Marazziti et al. 2010) indicates the presence of differences in gender and age: women have a worse performance than men in the tests of cognitive threshold and visual appeal (Sàrosi et al. 2008); the young subjects have an impairment of episodic memory, while patients with late onset have a greater involvement of executive functions and speed processing (Herrmann et al. 2007).

According to Thomas and Marazziti (Thomas et al. 2009 and Marazziti et al. 2010), cognitive impairment seems significantly higher in the old patients, especially in learning and verbal memory. In addition, a later onset is associated with worse cognitive impairment. This finding could be explained by the physiological process of aging that produces a neurocognitive pattern similar to depression.

It is possible that the presence of other comorbidities in the elderly, especially cardiovascular and cerebrovascular diseases, accounts for a reduction of the intellective performances, which are worsened by recurrent episodes of depression. So this kind of vulnerable patients needs an early treatment in the depressive phases.

Other studies showed that the processing of negative emotions, associated to a typical perception of inadequacy of one's actions, constitute an essential part of cognitive distortion during depression (Seligman, 1972). There is a bias in processing of stimuli, that is suitable to mood variations, which depends on individual history and the occurrence of depressive illness. In a review Gotlib (Gotlib and Joormann 2010), to this end, identifies the mechanisms underlying the relationship between cognitive biases and depression in the inhibitory processes and working memory deficits, as well as the inability to use adaptive responses to life events, whether positive or negative. This observation seems to be confirmed by the study of Keers (Keers et al. 2010): the occurence of SLEs is associated with a depressive episode where cognitive symptoms dominate the clinical picture.

Gotlib (Gotlib & Hamilton 2008) underlines that the most recent literature is beginning to identify the neural circuitry of emotion (Ochsner & Gross 2008) and in particular brain structures involved in depression (Cooney et al. 2007). These studies have documented the involvement of the limbic system, including the amygdale, the hippocampus and the anterior cingulated cortex in the experience of the emotional states and depression, as well as the dorsolateral prefrontal cortex in the regulation of emotions.

In conclusion, cognitive functions and their importance in daily life should be taken into a great consideration because of their functional impact on patients and because of the effects on psychiatrist's choices in terms of medical and rehabilitative treatment.

Depressed subjects have low performances in intelligence tests, although this is not considered as a primary deficit but secondary to the alterations related to memory deficits, attention and psychomotor skills. Studies showed that people with depression have alterations in both verbal and spatial memory. Although sometimes there are conflicting data, impairment is frequently reported in the acute phases of illness. Depression is associated with the impairment of everyday life functions, a reduction of job performances, especially in terms of productivity.

Traditionally, that impairment is seen as an effect of affective symptoms, but it was found that the improvement of depressive symptoms is not associated to the same improvement on daily activities. Moreover, these deficits could persist even in remission.

Neurocognitive deficits, related to a depressive condition, could have interesting implications in the clinical approach. The promotion of the adherence to treatment in patients (with recurrent or resistant forms of depression) and the improvement the quality of the therapeutic relationship are preconditions for the success of psychological support interventions or Integrative Psychotherapy. The use of cognitive training could be a valuable aid in the long-term treatment of depression in order to prevent relapses and improve the quality of life.

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