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Research report

Cognitive and psychomotor effects of three months of escitalopram treatment in elderly patients with major depressive disorder

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ABSTRACT

Background: Although psychomotor retardation (PR) and cognitive disfunctioning are essential symptoms of elderly depressed patients, the differential effect of treatment with an SSRI in the elderly on these symptoms has hardly got any attention in studies with objective experimental measures. Since effects appear relatively slower in elderly, this study evaluates the effect on cognitive and psychomotor functioning as compared to mood, on four points during a twelve week follow up of monotreatment with escitalopram.

Method: 28 non-demented elderly unipolar depressive patients on 5–20 mg escitalopram were compared to 20 matched healthy elderly. All participants underwent a test battery containing clinical depression measures, cognitive measures of processing speed, executive function and memory, clinical ratings of PR, and objective computerized fine motor skill-tests at the start and after 2, 6 and 12 weeks. Statistical analysis consisted of a General Linear Model (GLM) repeated measures multivariate analysis of variance of completers to compare the psychomotor and cognitive outcomes of the two groups.

Results: Although, apart from the significant mood effect, no interaction effects were found for the psychomotor and cognitive tasks, the means in general show a trend of differential effects in cognitive and psychomotor functions, with smaller effects and delayed timeframes and with presence of subgroups compared to mood effects.

Limitation: Longer follow up studies are necessary to evaluate differential long term effects.

Conclusion: In elderly, moderate effects of SSRI treatment on mood precede slow or limited effects on cognition and psychomotor retardation.

1. Introduction

Selective Serotonin Reuptake Inhibitors (SSRIs), and especially escitalopram and sertraline appear to be the first choice antidepressant pharmacological treatment for Major Depressive Disorder (MDD) (Cipriani et al., 2009), given their favorable balance between benefits (Cipriani et al., 2009; Kok et al., 2012), tolerability (Kasper et al., 2005; Mao et al., 2008; Gorwood et al., 2007; Bose, Li and Gandhi, 2008), and acquisition cost.

Psychomotor symptoms have clinical relevance and they are indicative of melancholic depression with or without psychotic features, and could be relevant in the choice of antidepressants (Schrijvers et al., 2008). In psychomotor functioning, three domains are generally distinguished: fine versus gross motor functioning, and speech functioning (Bennabi et al., 2013; Buyukdura et al., 2011; Schrijvers et al., 2008; Sobin and Sackeim, 1997).

Despite the importance of the psychomotor symptom cluster and the widespread use of SSRIs in the treatment of MDD, only few studies have investigated the impact of SSRIs on Psychomotor Retardation (PR). Some of these studies applied subjective observer-rated methods such as the retardation item of the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) and the Salpêtrière Retardation Rating Scale (SRRS) (Widlöcher and Ghozlan, 1989), whereas very few used an objective measurement method (Greden and Carroll, 1981), a battery of figure copying tasks with the use of a pressure-sensitive pen and a digitizer. The latter technique results in objective and real-time recordings of perceptual motor activity and enables to distinguish between the cognitive and motor processes involved in a writing movement.

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Hegerl et al. (2005) and Mergl et al. (2004) reported an increase in velocity of rapid hand movements after treatment with [reboxetine and] citalopram, applying such a computerized test battery during a 4-week treatment. Sabbe et al. (1996) treated depressed inpatients, for whom other psychotropic medication was restricted to the absolute minimum, during six weeks with fluoxetine 20 mg and observed an overall cognitive but no motor improvement on a battery of digitized writing tasks. Using the same drawing tasks, Schrijvers et al. (2009) compared the psychomotor performance of 22 MDD inpatients to a control group of 19 healthy subjects to evaluate during 6 weeks the effect of treatment with 50 mg sertraline, while ruling out effects of other psychotropic medication. They found decreased cognitive and motor times in patients for copying simple lines or figures, but no decrease in motor times for drawing more complex figures, with a higher cognitive load for motor planning.

Depression presents differently in elderly, with less mood complaints and more somatic, psychomotor and cognitive symptoms (Alexopoulos et al., 2002). Moreover, depression may be secondary to a different medical condition or drug, entailing more risk of drug–drug and drug-disease interaction and adverse effects of medication. In addition, aging itself causes decline in psychomotor and cognitive functioning (Alexopoulos et al., 2002). PR is a particularly relevant symptom cluster, given its direct relationship with loss of activity and functioning in daily life (Santos et al., 2012), reduced self-care, and higher risk of falling (Chen et al., 2012). It would even be bi-directionally associated as a risk-factor for and as a result of depression. Moreover, PR is more distinct in elderly (Parker et al., 2000, 2001), and characteristic for the dysexecutive syndrome (Lockwood et al., 2002). Finally, PR predicts poor treatment response and chronicity of geriatric depression (Kalayam and Alexopoulos, 1999).

SSRIs are efficacious, but elicit a delayed response in depression in elderly, compared to younger patients (Kok et al., 2012; Topiwala et al., 2014). In the very old, SSRIs are more effective than placebo, but only in severe depression. Important differences in results were found with ranges of 18 to 82% for placebo and 16 to 80% for citalopram (Roose et al., 2004). Finally, SSRI reduces the relapse rate significantly (Gorwood et al., 2007), known to be higher in elderly patients (Mitchell and Subramaniam, 2005).

Non-responders to SSRIs appear to be a subgroup with standard cognitive impairments (Culang et al., 2009). Citalopram-treated patients with deficient response inhibition show an even worse response than placebo-treated patients. With intact response inhibition, on the contrary, results are the reverse (Sneed et al., 2010).

This study will investigate the differential effects of escitalopram on cognitive and psychomotor measures in elderly patients and compare them to mood effects, without interfering effects of other psychotropic medication. Since effects of SSRIs in elderly are slower, the timeframes of the various symptoms were also compared. Drawing on previous research, we hypothesize, apart from a decrease in depressive symptoms, a decrease of motor time in simple motor tasks (Hegerl et al., 2005; Mergl et al., 2004), an improvement of all cognitive measures and of cognitive initiation times (Sabbe et al., 1996), but no improvement of motor times in complex motor tasks involving more motor planning (Schrijvers et al., 2009). Further, we explore the possibility of the existence of subgroups in elderly patients, based on processing speed.

2. Materials and methods

For a full description of the study population, inclusion and exclusion criteria, assessments and tasks and baseline results, see the baseline report of this investigation (Beheydt et al., 2015).

Twenty-eight non-demented (Mini Mental State Examination (MMSE) Score >24) elderly (age >60) medication-free in- and outpatients with unipolar single episode or recurrent MDD (score on Geriatric Depression Scale (GDS) >11; Yesavage and Brink, 1982) were compared to 20 healthy controls, matched for age, gender, education and vascular risks.

All participants were administered a questionnaire about health, medication, wellbeing status and educational level. Next, the MMSE (Kok and Verhey, 2002) and GDS were administered. After inclusion, the cognitive and psychomotor functioning of this group were compared to those of the healthy elderly at four time points (T) after the start of treatment with escitalopram 5–20 mg: at baseline and at week two, six and twelve. All assessments took place in the afternoon.

Clinical depression severity was assessed using the GDS (30 items) (Yesavage and Brink, 1982), whereas the State and Trait Anxiety Inventory (STAI 1, STAI2) (Spielberger et al., 1983) informed about the degree of anxiety symptoms. The 15-item Salpêtrière Retardation Rating Scale (SRRS) (Widlöcher and Ghozlan, 1989) was administered to assess the clinical level of psychomotor retardation.

For the objective psychomotor assessment, participants were asked to copy lines (CL) or figures (CF) from a computer screen with the use of a special pressure-sensitive pen and a digitizer (Maarse et al., 1988). The initiation time (IT), the time between the presentation of the stimulus and the start of the first drawing movement, and the motor time (MT), the time from the start of the first drawing movement to the end of the last drawing movement, were calculated. In the second task, the reinspection time (REIN T), the time from retouching the starting spot to resuming starting the drawing, was also determined. Reinspection time was not included in the motor time. For the Symbol Digit Substitution Test (SDST) (Mc Leod et al., 1982), the same recording techniques were used as with the copying tasks. The following variables were analyzed: the number of correct answers (SDST NCORR), the matching time, i.e., initiation time (SDST IT), and the writing time, i.e., motor time (SDST MT).

Cognitive functioning was assessed using the computerized Wisconsin Card Sorting Test (WCST; Barceló and Knight, 2002; Greve et al., 2002). Indices used were the number of correct answers (WCST NCORR) and the number of categories (WCST CAT) completed. Additionally, from the Stroop color-word test (Mc Leod, 1991) the variables reading speed (Stroop1) and interference (Stroop INT) were analyzed. From the 15-words verbal memory test (Saan and Deelman, 1986), only the number of correct recalls in the fifth trial (15W TOT) was recorded (Verbal Memory Total). The delayed recall was scored as 15W RECALL. For the Verbal Memory Recognition too, only correct recognitions (15W RECOG) were scored.

Statistical analysis of the data was performed using SPSS 17.00. and consisted of a General Linear Model (GLM) repeated measures completers analysis to compare the psychomotor and cognitive outcomes of the two groups on all assessment moments, with Time as within-subjects factor and Group as between-subjects factor (Field, 2009). When sphericity could not be assumed, the Greenhouse Geisser correction was used to reduce Type 1 errors. Effect sizes were calculated with partial η^2. Completers analysis was chosen because of the known high variance between and within patients, which makes estimations inappropriate. However, in order to rule out completers bias, the power could be improved by a Last Observation Carried Forward (Supplement Table 3), because drop out patients never got better afterwards and the risk of Type 1 errors was non-existent. The LOCF was only used to check the reliability of the data found in the completers group (Supplement Table 1). Subsequently, an exploratory analysis tested for differences between patients with high (<28) and low level