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Research Article

Selective Serotonin Reuptake Inhibitors for Mild Cognitive Impairment: A Systematic Review

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Abstract

Background and purpose: Mild cognitive impairment (MCI) can be the first sign of impending dementia, particularly Alzheimer's disease (AD). Selective serotonin reuptake inhibitors (SSRIs) could potentially impact on the neurodegenerative process of MCI and enhance memory and cognition by promoting neurogenesis in the hippocampus. The aim of this study was to systematically review randomised, placebo-controlled trials of SSRIs in patients with MCI.

Methods: The authors systematically reviewed literature on the efficacy and safety of treatment of MCI with SSRIs to determine if treatment with SSRIs reduced the rate of cognitive decline in such patients, compared with a placebo intervention. MEDLINE (from 1948 to March 2013), and EMBASE (from 1980 to March 2013), were searched in March 2013 for publications relating to SSRIs and MCI. One author screened titles and abstracts and obtained full texts of potentially eligible studies. Full papers were scrutinised independently by both authors to determine whether they fulfilled the inclusion criteria.

Results: Of 4480 abstracts screened, 48 full texts were retrieved for scrutinisation. Of these, one study met the inclusion criteria. It comprised 58 participants with MCI , who were randomised to either fluoxetine 10mg/day, increased to 20mg/day after 1-2 weeks for a duration of 8 weeks, or placebo and were followed up for the duration of the treatment but not after treatment had ended. Cognition was significantly better in the fluoxetine group compared to placebo at the end of treatment. There was a high drop-out rate, particularly in the treatment group.

Conclusions: The study identified showed that patients allocated fluoxetine had better cognition at the end of treatment compared to the placebo group. However, the sample size was small and further randomised clinical trials are needed to confirm whether fluoxetine in MCI reduces the rate of cognitive decline and whether any beneficial effects are sustained after treatment ends.

INTRODUCTION

Description of the condition

Mild cognitive impairment (MCI) may be the first sign of impending dementia, particularly Alzheimer's disease (AD). It can be diagnosed according to the Petersen Criteria [1]. The rate of progression to dementia varies considerably between individuals, with some patients never advancing to established dementia. Treatment in the early stages of MCI may delay progression to dementia.

Dementia is a clinical syndrome that is characterised by an acquired, progressive decline in cognition that occurs over a period of months to years. It affects approximately 5% of those aged over 60 rising to about 30% of those over 85 [2]. As the proportion of older people in the population increases, it is estimated that the prevalence of dementia in the UK will double in the next 30 years [3].

Description of the intervention

Selective serotonin reuptake inhibitors (SSRIs) have been shown to be effective in the treatment of depression [4]. This

class of drugs includes fluoxetine, sertraline, paroxetine, citalopram and fluvoxamine. SSRIs are highly selective for the neurotransmitter 5-hydroxytryptamine receptor (5HT; serotonin receptor). Depression is thought to be associated with a functional deficit in 5HT. SSRIs act to improve mood in depression by increasing the extracellular levels of the 5HT by inhibiting its reuptake into the presynaptic cell. Over the years the therapeutic uses of have become more diverse, being used successfully to treat other conditions such as obsessive–compulsive disorder [5], panic disorder [6] and bulimia [7]. There has also been recent evidence regarding their potential in stroke recovery. Plausible mechanisms of action (other than enhancing mood), include neurogenesis, neuroprotective effects and indirect effects on the adrenergic system, through upregulation of beta 1 receptors [8].

How SSRIs might reduce the rate of cognitive decline in people with MCI

Current treatment of dementia targets the cholinergic system. However, there is evidence to suggest that other neurotransmitters contribute to age-related cognitive decline in addition to cholinergic dysfunction [9,10,11]. Other neurotransmitters, including serotonin interact with the cholinergic system, thereby playing a role in cognitive processes [12]. Furthermore, it has been reported that the degree of cholinergic activation required in keeping the brain active could be reduced by a concurrent activation of the central serotonergic transmission [13]. SSRIs could have a potential impact on the neurodegenerative process of MCI and help to enhance memory and cognition by promoting neurogenesis, since they have a neurotrophic effect and neurotrophins are vital for nerve regeneration. Increased neurotrophin expression in the hippocampus has been demonstrated with SSRIs [14]. Animal studies have demonstrated that SSRIs promote dendritic branching and neurogenesis in adult rats [15,16]. Migration of new neurones to damaged areas of brain has been found to occur with SSRIs [17] in addition to neurogenesis within damaged areas [18]. Indeed, in Alzheimer's dementia, reduced levels of serotonin and its precursors such as tryptophan have been convincingly demonstrated [19]. SSRIs also have a neuroprotective effect, through repressing microglial activation, thereby decreasing inflammation [20], as well as enhancing the expression of specific proteins such as hypoxia inducible factor 1 alpha [21]. SSRIs have an indirect effect on the adrenergic system, through up-regulating beta-1 receptors [22]. Cortisol dysregulation has been associated with cognitive decline [23,24,25]. Treatment with SSRIs leads to decreased cortisol secretion, which has been associated with improvement in some cognitive domains [26,27]. Several studies have demonstrated improvement in cognitive function in patients with AD treated with SSRIs [28,29]. However, the role of these agents in the treatment of MCI is currently unclear, and worthy of investigation if they can prevent loss of independence and cognitive decline in such patients. There is no systematic review, to our knowledge, of SSRIs for MCI.

Aims

To determine whether, in patients with MCI, treatment with an SSRI is associated with better cognition at the end of treatment than those allocated to a placebo, and whether there is evidence of other benefits such as improvement in mood and whether there is an excess of adverse events.

A systematic review is the least biased method of combining data from different studies as it uses explicit systematic methods. Systematic reviews and meta-analyses are better than individual studies in informing clinical practice as they combine the information from relevant studies and can give more precise estimates of the effects of health care. Meta-analyses have the advantages of an increase in power, precision, the ability to answer questions not posed by individual studies, and the opportunity to settle controversies arising from conflicting claims. The results must be interpreted critically, however, bearing in mind any within-study biases, variation across studies and reporting biases [30].

Study question

We performed a systematic review of the literature to determine the effect of an SSRI compared to placebo on cognition in patients with MCI, whether an SSRI influences disability and dependency or improves mood, and whether treatment with an SSRI is associated with an excess of side effects including morbidity and mortality.

MATERIALS AND METHODS

Criteria for considering studies for this review

We included placebo-controlled, double-blinded, randomised studies involving SSRIs, published as abstracts only or full texts.

Types of participants

Trials had to recruit individuals with MCI as defined by each study, but in accordance with the generally accepted criteria of a subjective memory complaint with relatively preserved daily functioning. Studies including patients with delirium or established dementia were excluded. We included studies that used SSRI in MCI, irrespective of what the primary aim of the study was.

Types of interventions

Any trial that used a drug classified as SSRI such as citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline, irrespective of treatment duration, route of administration or dose was included. Only trials that compare SSRI to placebo were included. Those that used other antidepressants or used comparisons with other alternative active treatment were excluded.

Outcomes

We were interested in outcomes at the end of treatment, and at the end of any follow-up. The primary outcome was cognitive performance that had been formally accessed by recognised scoring systems including, but not limited to Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog) [31], Mini-Mental State Examination (MMSE) [32] and Clinical Dementia Rating sum of the boxes (CDR) [33].

Secondary efficacy outcomes are agitation and psychosis, mood as measured on various dementia scales, patient's ability to perform activities of daily living, adverse events, care giver's

distress, dropping out of the study for any reason (including death).

Search Methods for Identification of Studies

The authors systematically reviewed the literature on the efficacy and safety of treatment of MCI with SSRIs.

Electronic Searches:

The following electronic bibliographic databases were searched:

- MEDLINE (from 1948 to March 2013), searched March 2013
- EMBASE (from 1980 to March 2013), searched March 2013

The MEDLINE search strategy was developed and adapted for the EMBASE database. In addition, the online database, Current Controlled Trials (www.controlled-trials.com) was searched (April 2013)

Searching other resources: In an effort to identify further published, unpublished and ongoing trials, reference lists of included trials and relevant reviews were searched when full text were retrieved for detailed scrutiny.

Data Extraction and Management: A data extraction form was developed and data extraction was performed by one reviewer, including the risk of bias. The following data were extracted:

1. The report: Author, title, year and source of publication
2. The study: Setting, type of study, stated aims, stated outcomes.
3. The participants: Number, age, gender, severity of MCI, other psychiatric illness, current level of cognition and independence.
4. The intervention: Type, duration, dose, timing and mode of delivery.
5. The outcomes: For experimental and control group.

The quality of each study included was considered based on the Cochrane's reviewer's handbook [30]

Assessment of risk of bias in included studies: Risk of bias was assessed with guidance from the Cochrane Handbook for Systematic Reviews of Interventions. It was determined whether there was allocation concealment; how randomisation was performed (sequence generation method); whether there was blinding of patient, personnel and outcome assessors; whether there were incomplete outcome data and whether there was selective outcome data reporting. For each possible source of bias, the study was categorised as low risk, high risk or unclear risk.

Measurement of treatment effect: Statistical analysis was performed using the Review Manager software, Revman 5.1. A summary statistic for each outcome measure as calculated to describe the observed treatment effect at the end of the intervention.

Dealing with missing data: The primary investigator was contacted through email in an attempt to obtain missing data.

Assessment of Heterogeneity: We intended to assess heterogeneity using the I^2 statistic.

Assessment of reporting bias: By scrutinising the aims and methods of the trial and comparing these with the outcomes reported, selective reporting of results was checked for. We attempted to find published protocols.

Data Synthesis: Standardised mean differences (SMD) were used to estimate treatment effects for continuous variables, with 95% confidence intervals (CIs). The observed treatment effect at the end of the intervention was presented in a Forest plot, using Revman 5.1, for each outcome measure, using continuous variables. If we had dichotomous variables, we would have used risk ratios.

Data Collection and Analysis

Selection of studies: The searches of MEDLINE and EMBASE were run and the resulting references were downloaded onto Mendeley. At this point some duplicate references were removed automatically. Further scrutiny of each citation resulted in the removal of further duplicates. The resulting titles and abstracts were then examined by one author and any obviously irrelevant reports were excluded. Full text articles of potentially eligible studies were obtained and inclusion and exclusion criteria applied by two authors, independently.

RESULTS

Figure 1 shows the number of unique references identified by the searches, the number of records excluded after preliminary

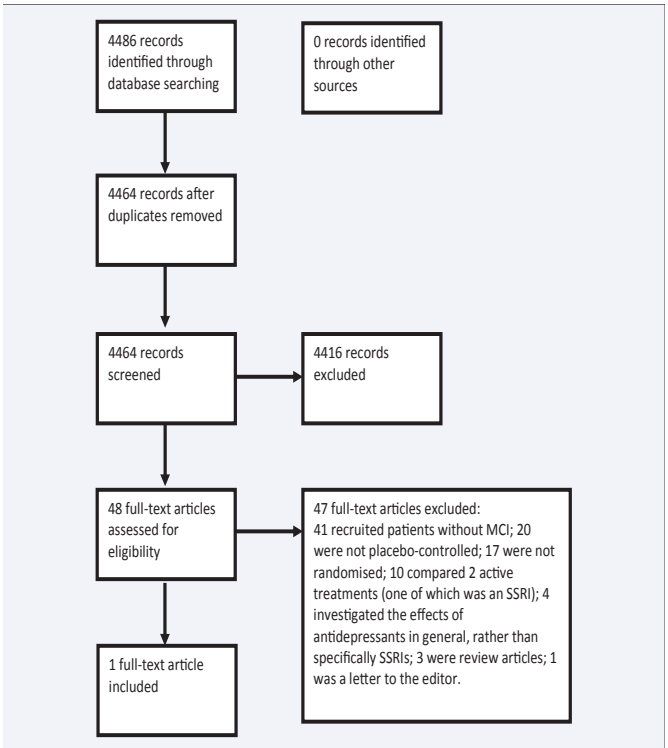

Figure 1 Study Flow Diagram.

screening of abstracts, and the number of records retrieved in full text, whilst tables 1 and 2 demonstrate the characteristics of the included and excluded studies.

Of the 4464 citations initially identified, 48 full texts were retrieved, one of which fulfilled the inclusion criteria. It aimed to determine whether treatment of patients with MCI with fluoxetine had any effect on cognition. It randomised 58 patients with MCI to SSRI or placebo and the patients randomised to the SSRI group were treated with fluoxetine 10mg/day initially, which was then increased to 20mg/day after 1-2 weeks for a total duration of 8 weeks. The placebo pill was identical in appearance and dosing regime [34]. Patients were those who had been referred to the Hafez Rehabilitation Center, Shiraz, Iran, for memory disturbances between June 2004 and September 2005. Participants in the study were diagnosed with MCI according to Petersen criteria and were required to have a score of 0.5 on the Clinical Dementia Rating scale whilst their MMSE score had to be below the adjusted score for age and education. The mean age of patients in the trial was 63.4 years and ranged from 55-75. The trial excluded patients who could not consent for themselves, patients with a past history of other major psychiatric disorders, including depression, neurological disorders and dementia. Outcomes recorded included Mini Mental State Examination (MMSE) and Wechsler Memory Scale II subtests, including immediate and delayed logical memory, digit span forward and backward, and family pictures I and II. These outcomes were recorded at baseline and after 1, 4 and 6 weeks of treatment, and finally at the end of treatment after 8 weeks treatment. Patients were not followed up after treatment and adverse events were not systematically recorded. The risk of bias for the included study is summarised in table 1.

In total, there were 47 excluded full-text studies. The following studies were excluded: Non-randomised comparisons of SSRIs and control; studies that compared 2 active treatments; studies that compared other antidepressants; and studies that recruited patients that did not meet the generally accepted definition of MCI (subjective memory complaint with relative preserved functioning). Figure 1 describes why these studies were excluded and table 2 details the characteristics of each excluded study. No studies were identified that compared SSRI plus usual care with usual care alone.

In the included study, patients in the fluoxetine group showed improvement in cognition at the end of treatment compared with placebo, demonstrated by improvement global cognition in MMSE (27.00 vs 24.1, P 0.002). Figure 2 illustrates the differences in MMSE scores between the fluoxetine group and placebo group at the end of treatment. The standard deviation at the end of treatment was 1.5 in the experimental group and 1.5 in the placebo group. For specific cognitive tests, scores were better at the end of treatment in the fluoxetine than the placebo group for immediate (10.82 vs 7.62, P 0.006) and delayed (9.28 vs 5.95, P=0.001) logical memory scores of Wechsler Memory Scale III (WMS-III). However, there were no significant differences between the two groups for digit span or immediate and delayed family picture scores in digit span (P 0.762, 0.162 and 0.072 respectively). The mean MMSE scores at the start and end of treatment were 24.17 and 27.00 respectively for the fluoxetine group, and 23.50 and 24.1 respectively for the placebo group. Since the trial is so small, it is possible that the apparent benefits seen in the fluoxetine group are higher because they started at a higher baseline MMSE. Data for agitation and psychosis, mood, ability to perform activities of daily living, adverse effects of medication and changes in caregiver's distress were not reported. Patients were not followed up after the 8 week period of treatment had finished. 14 patients dropped out of the study, 10 from the fluoxetine group, and 4 from the placebo group. Reasons for dropping out were not systematically reported in the study. The authors state in the report that the dropouts were mainly due to side effects, but they do not clarify the nature of such side effects.

DISCUSSION

We identified one trial, comparing an SSRI with control. It appeared to show beneficial effects of SSRIs on our primary outcome (cognitive performance) at the end of treatment, however, there were so many drop outs in an already small sample size, that it is difficult to draw any conclusions. Our secondary outcomes were not investigated in this study. The Fluoxetine group experienced a higher rate of drop-outs than the

Table 1: Risk of bias.

Source of Bias	Author's judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not explicitly stated.
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not explicitly stated.
Blinding of participants and personnel (performance bias)	Low risk	Placebo capsules had same shape, size and colour as fluoxetine and followed the same dosing procedure.
Blinding of outcome assessment (Detection bias)	Unclear risk	Not explicitly stated whether outcome assessors were blind to participants' allocations.
Incomplete outcome data (attrition bias)	High risk	Discussion mentions improvement in Clinical Global Impression, quality of life and behaviour. It is not stated in the method that these were going to be measured and there are no references to these measures in the results. Of the 58 participants who provided informed consent and were randomised to treatment, 44 completed the trial and underwent outcome assessment. The number of subjects who completed the trial in the groups of fluoxetine and placebo were 23 of 33 and 21 of 25 respectively.
Selective reporting (reporting bias)	Unclear risk	All outcomes noted in the methods were reported in the results. There is no published protocol for the study.
Other bias	Unclear risk	There were no significant differences in baseline statistics between the experimental and control group. Source of funding or drug company involvement not ascertained.

Table 2: Characteristics of excluded studies.

Study	Patients Recruited	Randomised trial?	Comparison Arm
Alves 2007	Patients with major depressive disorder and heart failure	No	Non-depressed heart failure patients and healthy controls.
Barch 2012	Patients with late-life depression	No	None
Bowie 2012	Adolescents and young adults at high risk of developing psychosis.	No	None
Cassano 2002	Elderly depressed patients.	Yes	Paroxetine compared to fluoxetine.
Claypoole 1998	Depressed HIV-1 seropositive outpatients.	Yes	Placebo
Constant 2005	Depressed outpatients.	No	Healthy control
Conti 1988	Hospitalised depressed patients	Yes	Placebo
Culang 2009	Depressed patients over the age of 75.	Yes	Placebo
Cunningham 1994	Patients with major depression	Yes	Venlafaxine vs trazadone vs placebo.
Dawes 2012	Patients with schizophrenia or schizoaffective disorder and sub-syndromal symptoms of depression.	Yes	Placebo
Dobkin 2010	Patients with Parkinson's disease and major depression or dysthymia	Yes	Notriptyline and placebo.
Fann 2001	Patients with mild traumatic brain injury.	No	None
Feighner 1999	Patients with major depression.	Yes	Placebo
Gala 2008	Review article into cognitive impairment and depression in the elderly.		
Gallassi 2006	Patients >50 with major depression.	No	Fluoxetine vs reboxetine
Geretsegger 1994	Elderly depressed patients.	Yes	Fluoxetine vs paroxetine.
Goveas 2012	Cognitively healthy postmenopausal women with depressive symptoms.	No	None
Han 2011	Patients with major or minor depression	No	Citalopram vs sertraline vs paroxetine
Herrera-Guzman 2010a	Patients with major depressive disorder	No	Duloxetine
Herrera-Guzman 2009	Patients with major depressive disorder.	No	Duloxetine.
Herrera-Guzman 2010b	Patients had major depressive disorder.	Yes	Placebo
Hindmarch 2010	Review article into effects of fluvoxamine on cognition and depression.		
Hinkelmann 2012	Patients with major depressive disorder	No	Healthy control group
Jorge 2010	Patients with stroke in previous 3 months.	Yes	Placebo and problem-solving therapy.
Kalechstein 2013	Cocaine-dependent individuals.	Yes	Modafinil and combination modafinil plus escitalopram.
Mandelli 2006	Patients with mood disorders.	No	None
Mendels 1999	Depressed outpatients.	Yes	Placebo
Mikami 2011	Patients with stroke in previous 6 months.	Yes	Placebo
Mohs 2012	Patients with fibromyalgia	Yes	Placebo
Mowla 2007	Patients with Alzheimer's dementia	Yes	Placebo
Narushima 2007	Patients with stroke in previous 6 months	Yes	Placebo
Nebes 1999	Geriatric patients with major depression.	No	None
Nebes 2003	Geriatric patients with major depression.	No	None
Niitsu 2012	Patients with schizophrenia.	Yes	Placebo
Pariante 2012	Participants were healthy males aged 18-33.	Yes	Placebo
Popp 2011	Review article into recent developments in the pharmacological treatment of dementia and MCI.		
Portella 2003	Patients with late-onset major depression aged >60.	No	Elderly healthy comparison.
Reilly 2011	Patients with major depression	Yes	Placebo
Robinson 2000	Patients with acute stroke.	Yes	Nortriptyline and placebo.
Savaskan 2008	Patients with current major depressive episode.	No	Healthy age-matched controls.
Savaskan 2009	Patients with current major depressive episode.Patients not defined as having MCI.	No	Healthy age-matched controls.

Simis 2006	Patients with acute supratentorial ischaemic stroke with major depression.	No	No treatment.
Sofronov 2011	Patients with paranoid schizophrenia aged 18-45.	Yes	Usual treatment with zuclopentixole.
Spalletta 2004	Letter to the editor		
Strik 2006	Patients with depression post-myocardial infarction.	Yes	Placebo
Tollefson 1993	Patients >60 with unipolar, non-psychotic major depression.	Yes	Placebo
Van Laar 2002	Participants were healthy volunteers aged 19-28.	Yes	Amitriptyline and nefazodone.

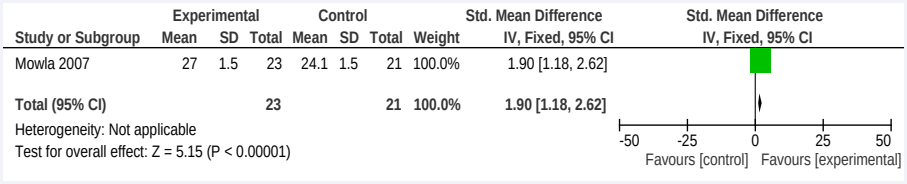

Figure 2 Forest plot comparing MMSE scores at the end of treatment in fluoxetine group vs placebo group.

placebo-group, but the precise reasons for non-completion are not stated. There were multiple sources of potential bias in this trial. For instance, it lacked details surrounding methodological aspects of the trial (sequence generation, allocation concealment, blinding, incomplete outcome reporting). This meant that the risk of bias was unclear. The funding source was not stated for this trial, which could be another potential source of bias. Side effects were noted as having occurred, but were not detailed or quantified in the record. The author was contacted with regards to missing data but no response was received.

After searching Medline and Embase, a higher than anticipated numbers of trials were identified, but the vast majority were obviously not relevant based on screening titles and abstracts. Therefore, we did not feel that more extensive searches of other databases would identify other papers. However, since only two online databases were searched, there is a possibility that some publications were missed. Three of the full texts obtained were review articles. These were not reviews of SSRIs for MCI, however, the reference lists were screened to add robustness to the search. Only one author screened the titles and abstracts from the MEDLINE and EMBASE searches. There is a small possibility that this single author may have missed trials. However, this author retrieved full texts of any publication that looked remotely relevant, and a second review author scrutinised all these full texts. Of the 48 full texts, only one was included.

No other systematic reviews of SSRI for MCI in either humans or animals were identified.

CONCLUSIONS

The data collected provides evidence of benefit of a single SSRI, fluoxetine, for improving cognitive performance in patients with MCI. However, data was only available from one small trial, with a high dropout rate, particularly in the fluoxetine group. Therefore, it is certainly not robust enough to make recommendations. The dropout rate amongst the treatment group was higher than the placebo group, which may mean that the apparent positive effects are spurious. Thus, we would not recommend the routine use of SSRI to improve cognitive performance in patients with MCI.

Currently, SSRIs are not prescribed with the aim of improving cognitive performance in patients with MCI. This review offered some evidence of the benefits of SSRIs in cognitive performance, including scores on MMSE and sub-tests of the WSM-III. Given that only one trial was identified, which was very small and had various limitations, it is evident that there is a need for a much larger randomised control trial involving SSRIs in MCI in order to determine the effect on cognition. Such a trial would need to be methodologically rigorous with a low risk of bias, with subsequent reporting to include comprehensive descriptions of all aspects of the methodology so the results can be interpreted and appraised.

This review found data only for fluoxetine treatment given over a period of 8 weeks. Given the variability in adverse effects and tolerability amongst different patient populations [35] it may be beneficial to investigate the effects of other SSRIs. As no follow-up data was available from this review, it is important that future research should report follow-up data to determine whether there is a sustained effect in comparison to the placebo group. Adverse events were not documented in the trial included in this review; therefore, future research must record all adverse events clearly. If such trials are implemented, it will be important to update this review with their results.

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