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Date: August 19, 2014

EFFECTS OF SECOND-GENERATION ANTIDEPRESSANTS ON COGNITIVE FUNCTIONS: A SYSTEMATIC REVIEW AND META-ANALYSIS

by

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ABSTRACT

Effects of Second-Generation Antidepressants on Cognitive Functions: A Systematic Review and Meta-Analysis

Objectives: Second-generation antidepressants are currently the first-line of treatment for depression and are widely used. The aim of this study was to determine the effects on cognition by second-generation antidepressants through a systematic review and meta-analysis of recent scientific literature.

Methods: Electronic search in Medline, PubMed, PsycINFO, CINAHL, and Embase for English-language abstracts from 1980 through May 2014, supplemented with a manual search from reference lists of relevant review articles was carried out to identify eligible studies. Studies were included if they met the following selection criteria: Population: adults (age≥18) with diagnosis of depression; Intervention: second-generation antidepressants (SGAD) marketed in the United States based on the American Hospital Formulary Service (AHFS) 2014 drug classification; Comparator: placebo or second-generation antidepressants; Outcomes: attention, processing speed, executive function and memory; and Study Design: Randomized Controlled Trials (RCTs) and observational studies. Data management and screening procedures were carried out by using RefWorks (ProQuest) and Microsoft Excel workbook. Data extraction and synthesis was conducted by the primary author using a data extraction form specially designed for this study. Studies were sorted according to type of neurocognitive test used and a minimum of 3 studies per test per study

design type was required in order to conduct further systematic review and meta-analysis. The methodological quality of the included studies was assessed by Cochrane risk of bias tool. A random effects model was used to estimate the pooled effects of antidepressant use on cognitive functioning. Heterogeneity was assessed by I2 testing. Egger's regression test and Trim and Fill method were used to examine for the presence of potential publication bias along with analysis of funnel plots. All analyses were performed using Comprehensive Meta-Analysis, v2.2 (Biostat, Englewood, NJ)

Results: A total of 4,274 abstracts were screened; 342 were retrieved for a full-text review. Of the reviewed full text articles, 17 (13 RCTs and 4 Observational) studies involving a total of 2,437 depressed patients) met the inclusion criteria. Studies were of optimum quality as assessed by the Risk of bias tool. Out of the 43 unique neurocognitive test; Mini-Mental State Exam (MMSE), Stroop Color Word test (SCWT), Choice Reaction Time Task (CRT) and Digit Symbol Substitution Test (DSST) were the most common tests used across the studies which fulfilled the selection criteria (minimum of 3 studies per test per study design type) for further systematic review and meta-analysis. Six studies were found eligible for inclusion into the meta-analysis for MMSE and the results were not significant with (SMD=0.126; 95%CI -0.046, 0.298; $p > 0.05$). There was no heterogeneity ($I2=0\%$, $p= 0.975$) and publication bias (Egger's regression intercept ($B_0= 0.29359$; 95%CI -1.04627, 1.63344; $p > 0.05$). Insufficient and inconsistent reporting of results involving SCWT, CRT and DSST prevented meta-analysis of study findings; hence, a systematic review was performed.

Four studies were found eligible for SCWT out of which two studies with positive findings which had a combined sample size of almost 13 times that of the non-significant study, which suggests improvement in executive function with second-generation antidepressants compared to placebo. The systematic review conducted on four studies which had used CRT suggests positive results with one study with sample size 30 times that of the non-significant study showing improvements in attention and processing speed in depressed patients treated with low dose second-generation antidepressants. The systematic review conducted on three studies which had used Digit Symbol Substitution Test suggested mixed evidence with two studies showing significant improvement in attention and processing speed with SMs compared to placebo while one study suggesting otherwise with SNRIs.

Conclusions: Meta-analysis of studies using MMSE suggests that SGADs do not affect global cognition but might affect other specific domains. Systematic reviews on studies involving SCWT, CRT and DSST suggest variable evidence regarding the effects of second-generation antidepressants on specific domains of cognition. However, there were indications of possible improvements in executive function, attention and processing speed with SGADs compared with placebo. Further studies involving reliable and widely used neurocognitive tests reporting necessary statistical detail for computing effect sizes are needed to estimate and quantify the effects of second-generation antidepressants on cognition.

Key words:

Second-generation antidepressants, cognitive function, systematic review, meta-analysis

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CHAPTER 1

INTRODUCTION

This chapter provides a brief overview of depression, cognitive function and the associated neurobiological changes in depression that affect cognition. In addition, it describes the second-generation antidepressants (SGADs) and their role in cognition in patients with depression.

Depression

Depression is one of the most common mental disorders in the world with a lifetime prevalence of 16.2%, 6.6% and 16.5%, 8.9% correspondingly for US and European women and men respectively (Alonso et al., 2004; Kessler et al., 2003). It is among the leading causes of disability in both developed and the developing world (Katona et al., 2014). It is associated with substantial morbidity, mortality and public health expense both in terms of direct and indirect economic costs (Kessler et al., 2003; World Health Organization, 2001). In addition, depression has been linked with reduced quality of life, impaired productivity, decreased social functioning and poor physical health (Katona et al., 2014). Even milder forms of depression, namely dysthymia or sub threshold depressive features, negatively affect activities and quality of life over the lifespan of the affected individual (Gotlib 1995 et al., 1995, Judd et al., 1994, 1996, 1997, and 2000). The Global Burden of Disease (GBD) studies in the past (Murray et al., 1996; WHO 2008, Mathers et al., 2002 and Ferrari et al., 2013) have made a remarkable contribution in gaining attention and highlighting the seriousness of

depressive disorders as a major cause of burden. This emphasis on depressive disorder has led to a positive change in elevating its rank in the hierarchy of public health agendas (Prince et al., 2007).

Cognitive Function

Cognitive function can be defined as the ability of the brain to procure, process, consolidate, store and retrieve information to enable the organism to adjust and manipulate his surroundings (Lechevallier-Michel et al., 2005; Han, 2006). According to Lezak et al., 2012 cognitive functions can be divided into four major classes which are akin to computer operations (Table 1.).

Table 1. Similarities between computer operations and cognitive functions

Computer operation	Cognitive function	Description
Input	Receptive functions	ability to select, acquire, classify and integrate information
Storage	Memory and leaning	Information storage and retrieval
Processing	Thinking	mental organization and reorganization of information
Output	Expressive functions	means through which information is communicated or acted upon

Although each function is discrete, they are interdependent and work in tandem, and are tough to divide in their pure individual form during their assessment by neuropsychological tests.

Cognitive functioning is generally evaluated through measuring various cognitive domains which include attention, executive function, memory and processing speed by a neuropsychological examination which involves getting to know the patient's background along with his current cognitive status and the use of a battery of screening test. Along with being an important gauge of cognitive functioning, the results of these tests are helpful for planning the anti-depressive treatment regimen and assessing its efficacy along with distinguishing between state and trait markers of depression (Marazziti et al., 2010).

Preferably a cognitive screening test should be fast, easy to score and interpret, effortless to administer by medical staff who are not physicians/psychologists/psychiatrists, not require special tools or training, have high sensitivity and specificity along with superb psychometric properties and be reasonably free from culture, educational, and/or language bias. (Slater and Young, 2013; Cordell et al., 2013)

Cognitive domains can be categorized into the following broad categories:

Attention

It is a selective process which streamlines the available information to highlight the most important part for subsequent processing (Milham, 2003)

Processing speed

It is the speed at which new information is processed by the brain to devise a response. Frequently administered neurocognitive tests to measure attention and processing speed are: Digit Symbol Substitution Test (DSST;

WAIS-R), Digit Span Forwards and Backwards (WAIS-R), Continuous Performance Task (CPT), Choice Reaction Time (CRT; CANTAB), Reaction Time (RTI; CANTAB), Simple Reaction Time (SRT; CANTAB), Trail-Making Test Part A (TMT A), Paced Auditory Serial Addition Test (PASAT), Serial Sevens Subtraction Test (SSST)

Executive function

It is an umbrella term that encompasses a broad class of cognitive processes that are essentially mediated by the frontal cortex that allows adaptive response to novel circumstances along with goal-directed behavior (Lezak et al., 2012; Burgess et al.,1998; Stuss et al., 1998; Miyake et al., 2000) The aforementioned novel circumstances comprise of situations that involve correcting errors, planning or decision making, reasoning and tackling problems which are of unknown or complex nature and resisting temptations (Marazziti et al., 2010).

Frequently administered neurocognitive tests to measure executive function are: Wisconsin Card Sorting Test (WCST), Trail-Making Test Part B (TMT B), Stroop Color Word Interference Test (SCWT), Categories Test, Block Design (WAIS-R), Picture Completion (WAIS-R), Concept Shifting Task (CST), Tower of London (TOL; CANTAB), Stockings of Cambridge (SOC; CANTAB), Intra/Extra dimensional Shift Test (CANTAB; IED), Spatial Span (SSP; CANTAB), Ruff Figural Fluency Test (RFFT), Verbal Fluency–Letter Fluency & Category Fluency, Controlled Oral Word Association Test (COWAT), The Delis-Kaplan Executive Function System (D-KEFS)

Memory

It refers to the ability of remembering and recalling information by the processes of encoding, saving and retrieving (Hofgren, 2009). It is further subdivided into: working, verbal and visual memory.

Working memory is responsible for holding limited amount of information which is thought actively (in real time) and made accessible long enough to utilize it. It is limited with respect to capacity and duration (Cowan, 2008). Verbal memory pertains to recollection of verbal information while visual memory is responsible for remembering of data which resembles objects, locations or surroundings.

Frequently administered neurocognitive tests to measure memory are:

Working memory: Arithmetic (WAIS-R), Digit Span Forwards and Backwards (WAIS-R), Delayed Recognition Span Test (DRST), Spatial Working Memory (SWM; CANTAB), Letter-Number Sequencing (LNS; WMS-R), Logical Memory (WMS-R), n-Back Test

Verbal learning and memory: California Verbal Learning Test (CVLT), Rey Auditory Verbal Learning Test (RAVLT), Rivermead Behavioral Memory Test (RBMT), Hopkins Verbal Learning Test Revised (HVLT-R), Logical Memory (WMS-R), Verbal Paired Associates (VPA;WMS-R), Visual Verbal Learning Test (VVLT), Digit Span Forwards and Backwards (WAIS-R), Luria Verbal Learning Test (LVLT), Serial Sevens Subtraction Test (SSST), Verbal Recognition Memory Test (VRM;CANTAB)

Visual learning and memory: Visual Reproduction (WMS-R), Benton Visual Retention Test (VRT), Benton Visual Form Discrimination (VFD), Rey-Osterrieth Complex Figure Test (ROCF), Kimura's Recurring Figures Test (RFT), Visual Verbal Learning Test (VVLT), Pattern Recognition Memory (PRM; CANTAB), Spatial Recognition Memory (SRM;CANTAB), Delayed Matching to Sample (DMS; CANTAB), Paired Associates Learning (PAL;CANTAB), Matching Familiar Figures Test 2 (MFFT-20)

Depression and Cognitive Function

Depression not only affects the way we function emotionally, but also the way we interact with the world (Francomano et al., 2011). On the cognition front, the capacity to think, focus, make decisions, form ideas, recollect and speed of processing are affected by depression (Marazziti et al., 2010; Reppermund et al., 2009). Cognitive impairment in terms of diminished ability to think or concentrate belongs to the operational criteria of diagnosis of major depressive disorders in ICD-10 and DSM-IV (APA 1994). Although many depressed patients do not complain having cognitive problems or even lack objective findings on cognitive assessments, studies show that depressed patients perform poorly compared to non-depressed patients on numerous neuropsychological measures (Veiel, 1997; Zakzanis et al., 1998). Along with MDD, patients with anxiety, OCD, panic disorder, ADHD, bipolar disorder, also experience impaired cognition as part of their illness (Gualtieri et al., 2008; Mantella et al., 2007; Willcutt et al., 2005; Purcell et al., 1998; Boldrini et al., 2005).

Neurobiological changes in depression affecting cognition

Various neurobiological anomalies in depression are pertinent to cognitive function (Kandel et al., 2000). Disturbed transmission in neurotransmitter systems in particular the serotonergic, noradrenergic, dopaminergic, cholinergic and GABA-ergic systems are responsible in the pathophysiology of depression (Kandel et al., 2000; Thase, 2000). There are four key hypothesized mechanisms which relate depression, neuronal function and change in cognition. Antidepressants interact with these mechanisms to alter cognitive functioning (Shelton et al., 2000).

Normalization of serum cortisol

Depressed patients have increased serum levels of cortisol for a prolonged period, which has a neurotoxic effect and is associated with memory problems along with loss of hippocampal volume (Thase, 2000; O'Brien et al., 2004; Sheline et al., 1999; Campbell et al., 2004; Egeland et al., 2005; Sauro et al., 2003). This increase in cortisol levels is caused by stress reaction which is per se present in depression or caused by malfunctioning in feed-back regulation of the Hypothalamic-Pituitary-Adrenal (HPA-) axis (Shelton et al., 2000; Thase, 2000). Prolonged use of antidepressants may lead to a diminution in serum cortisol levels (Shelton et al., 2000) and improvement in memory (Vythilingam et al., 2004).

Brain-Derived Neurotrophic Factor (BDNF) and Increased Neurogenesis

Animal models suggest that there is scanty neurogenesis in depression (Kandel et al., 2000; Hashimoto et al., 2004). Neurotrophins like BDNF mediate the elevation in neurogenesis during antidepressant use (Shelton et al., 2000; Hashimoto et al., 2004; Alme et al., 2007; Sapolsky, 2004).

N-Methyl-d-Aspartate- (NMDA-) receptors and Long-term Memory:

NMDA-Receptor activation is involved in the long-lasting potentiation that is pivotal for memory function (Shelton et al., 2000; Biringer et al., 2009)

Dopaminergic System and Attention

Lack of energy and enthusiasm noted in depression might be connected to low dopaminergic activity in the brain (Salamone et al., 2006). Antidepressants act on the dopaminergic system to increase its activity resulting in an improvement in arousal and attention (Monti and Monti, 2007; Chamberlain et al., 2006; Nicholson et al., 1990).

Functional neuroimaging studies in cognitive neurosciences have assisted in understanding the specific brain regions involved in neurophysiological defects and their relationship with cognitive functioning among depressed patients (Biringer et al., 2009; Drevets et al., 2000; Videbech, 2000; Silverstone et al., 2005; Steffens and Potter, 2008). The four important regions are:

Orbitofrontal cortex (OFC)

It is associated with discriminative processing of affective stimuli evidenced by the preferential and rapid response to melancholic over happy words (Elliott et al., 2002). Also neuroimaging studies have shown that elderly depressed patients have smaller total OFC volumes compared to non-depressed patients (Lai et al., 2000; Ballmaier et al., 2004).

Anterior cingulate gyrus (ACC)

Its cognitive role includes both, commencing (Nemeth et al., 1988) and restraining (Paus et al., 1993) of behavior through conflict monitoring (Carter et al., 2000) and assessment of motivational content (Devinsky et al., 1995). It is also connected with biased processing towards sad affective stimuli like OFC. Additionally, ACC also plays a part in spatial planning and working memory with depressed patients showing lesser activation of this region than non-depressed comparators (Elliott et al., 1997).

Dorsolateral prefrontal cortex (DLPFC)

It helps in execution of attentional control (Steffens and Potter, 2008). Patients with mood disorders show diminished left cingulate activation and increased left DLPFC activation for tests of response inhibition compared to non-depressed patients (George et al., 1997). DLPFC is also implicated for its role in working memory (Owen et al., 1999), episodic memory (Rugg et al., 1999), planning (Dagher et al., 1999), and response monitoring (Blakemore et al., 1998).

Hippocampus

It plays an important role in learning and recall. Shrunken hippocampal volume along with reduced performance on tests for episodic memory is seen in elderly individuals with depression (Hickie et al., 2005). Imaging studies show mixed evidence with respect to the relation between hippocampal volume and depression with some associating decreased volume with depression in adults (Sheline et al., 1996; Frodl et al., 2004) while others challenging this finding (Hastings et al., 2004). Hippocampal volume reductions are more commonly seen in individuals with recurrent depression (MacQueen et al., 2003; Sheline et al., 2003), early onset depressive disorders (Sheline et al., 1999; MacQueen et al., 2003), and with lengthy periods of untreated depression (Sheline et al., 2003).

Antidepressants and Cognitive Functioning

Biringer et al., 2009 proposed a theoretical model (Figure 1.) which assists in understanding the confounding and mediating factors involved in the relationship between antidepressants and cognitive function in depression. In the model, the associations between neurobiological changes, depressive symptomatology, cognitive function, and effect of antidepressants are complex and poorly understood. The connecting pathways and their effect directions are uncertain.

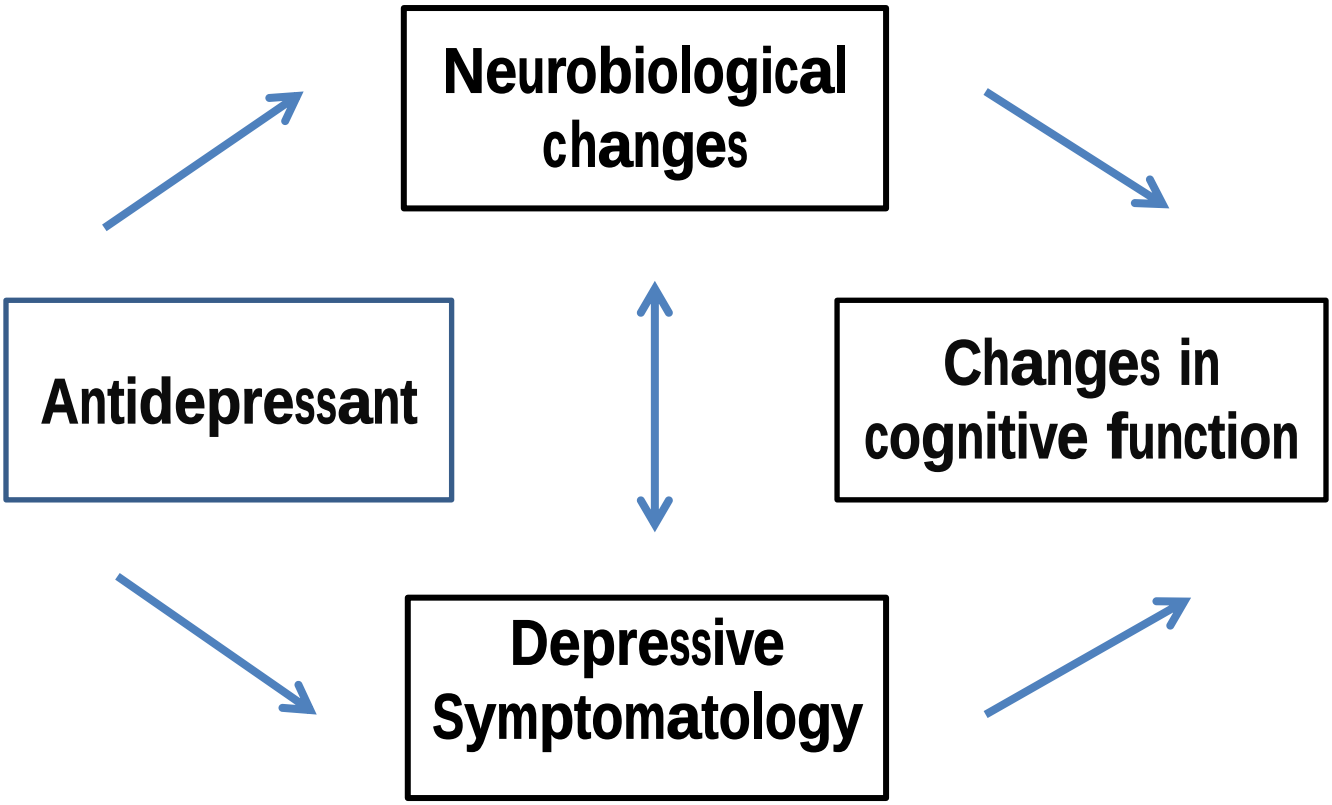

Figure 1. Theoretical model showing relationship between antidepressants and cognitive function in depression

The effect of antidepressants on cognitive function operates (via action on depressive symptomatology) by ameliorating the depressive symptoms which

results in decreased exhaustion and improvement in enthusiasm (Raskin et al., 2007). On the other hand, effect of antidepressant may also be due to their pharmacodynamic effects - mediation by neurobiological changes in the brain which further impacts cognitive functioning (Shelton et al., 2000). Also the change in cognitive function by antidepressants may be attributed to a placebo effect (Biringer et al., 2009).

Pharmacotherapy of Depression

Several treatment options are available for treating depression that can be broadly classified into psychotherapy and pharmacotherapy. Traditionally, antidepressants are often reserved to treat major depressions while cognitive and interpersonal psychotherapies are often used in the treatment of the mildly depressed patients (Dunner et al., 1994). Psychotherapy can include Cognitive-Behavioral Therapy (CBT), Interpersonal Psychotherapy (IPT), and Dialectical Behavior Therapy (DBT). Psychotherapy is not an efficient treatment option in the case of individuals where chemical imbalance is associated with depressive symptoms. Medications, mainly antidepressants, have been found to decrease symptoms of the disorder, thus making it useful treatment (Julien et al., 2005). In the past two decades, there has been a marked increase in the use of antidepressants that make them the third most commonly prescribed medication class in US (Olfson et al., 2009; Hsiao et al., 2010). Also with sales of around $20.4 billion globally, antidepressants are among the most-expensive and widely prescribed medication classes (IMS Health 2011).

Antidepressants are the cornerstone of treatment of moderate to severe depression and are often coupled with psychotherapy (APA 2000). In addition to their primary use in MDD, antidepressants are also used in treating other psychiatric illnesses like anxiety disorders: phobic disorders, panic disorder, obsessive-compulsive disorder, generalized anxiety disorder, post-traumatic stress disorder; attention deficit and disruptive behavior disorders. They are also used in gastrointestinal and genitourinary disorders like IBS and enuresis respectively. Additionally, antidepressants are also used in medical illnesses like pain syndromes: migraine headache, other chronic pain conditions; psychotic disorders: schizoaffective disorder; and sleep disorders: insomnia, night terrors, sleep apnea, narcolepsy, functional enuresis (Khawam et al., 2006).

Studies have shown that various types of antidepressants are equally effective in their action, and only select antidepressants are shown to be more effective than others (Montgomery et al., 2007; Hansen et al., 2005). Hence, the tolerability profile of antidepressants determines their selection (Knegtering et al., 1994)

Mechanism of action of Antidepressants and shift to SGADs

Antidepressants were introduced in the late 1950s with the primary motive to treat depression. The first antidepressants developed were Monoamine oxidase inhibitors (MAOIs) and Tricyclic antidepressants (TCAs) followed by SSRIs and other newer antidepressants during the recent decades. Both MAOIs and TCAs are effective antidepressants but have troublesome side effects.

MAOIs have a high incidence of deleterious interaction with some food and drugs. These interactions result in grave side effects and hence careful monitoring of the patient along with certain dietary restrictions are needed. This has led to a limited use of MAOIs as they are primarily reserved for the treatment of atypical depression and in patients who have a poor response to other antidepressants (Julien et al., 2005).

TCAs act by inhibiting the neuronal reuptake of norepinephrine and serotonin into presynaptic nerve terminals. Along with this action, they also block serotonergic, α -adrenergic, histaminic, and muscarinic receptors which are responsible for their adverse effects which include anticholinergic side effects like blurred vision, xerostomia (dry mouth), urinary retention, constipation, aggravation of narrow-angle glaucoma, and sinus tachycardia attributed to muscarinic receptors and orthostatic hypotension, dizziness, and reflex tachycardia attributed to α-adrenergic receptors (Clark, 2012). In addition, TCAs have a narrow therapeutic index and sedation, weight gain and sexual side effects are common during therapy. The sedative and anticholinergic effects shown by TCAs adversely affect cognitive function that displaces them from being the top choice for the treatment of depression (Campbell et al., 2004; Doraiswamy et al., 2003).

Advent of Second-Generation Antidepressants

During recent decades, SSRIs and other new antidepressants have gained increased popularity and have become the first line of treatment among

antidepressants mainly due to their low-side effect profile and better tolerability resulting in increased adherence to therapy (Barkin et al., 2000). Olfson et al., 2009 reports the decline in prescription of TCAs while an increase in recommendation for SSRIs and newer agents in the treatment of depression.

SSRIs block serotonin reuptake which leads to an increase in concentration of the neurotransmitter in the synaptic cleft further leading to increased postsynaptic neuronal activity (Clark, 2012). This selective targeting on serotonin reuptake (other receptors are left unaffected) results in fewer and less serious adverse effects compared to TCAs and MAOIs. Also they have a wide therapeutic index which makes them relatively safe in case of deliberate/ unintentional overdosing. Many studies have proven SSRIs to be better than older drugs with regards to cognitive function (Hale et al., 1995; Nebes et al., 2003; Doraiswamy et al., 2003). SSRIs along with their primary use depression are also effective for various psychiatric disorders like anxiety disorders, OCD, Generalized Anxiety Disorder (GAD), Post-Traumatic Stress Disorder (PTSD), panic disorder, and phobias (Dannewitz, 2008).

SNRIs in their mechanism of action are similar to TCAs in their blocking the reuptake of serotonin and norepinephrine but distinguish themselves from TCAs by their absence of receptor-blocking activity at α -adrenergic, histaminic, and muscarinic receptors.

This lack of affinity for the aforementioned receptors and the nonexistent effect on monoamine oxidase limits their side effects and improves their tolerability compared to TCAs (Lambert and Bourin, 2002).

Definition and classification

Second-generation antidepressant (operationally defined as non-TCAs and non-MAOIs) marketed in the United States classified under American Hospital Formulary Service® Drug Information 2014 (AHFS DI) classification categories from the American Society of Health-System Pharmacists (ASHP) was used to define antidepressants in conducting the systematic review. Antidepressants were categorized into selective serotonin reuptake inhibitors (SSRIs), selective serotonin- norepinephrine reuptake inhibitors (SNRIs), serotonin modulators, or miscellaneous agents.

Drugs were classified as follows:

SSRIs were citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline

SNRIs were desvenlafaxine, duloxetine, venlafaxine, milnacipran and levomilnacipran

Serotonin modulators were nefazodone, trazodone, vilazodone and vortioxetine

Miscellaneous agents were bupropion and mirtazapine

Literature Gap

The effects of antidepressant treatment on cognitive function in depressed patients have not been studied thoroughly. Although previous studies which synthesized the evidence of the effects of antidepressant on cognitive function have been carried out; nearly all of them were traditional narrative reviews which had just theoretically covered the various aspects of cognitive effects of antidepressant therapy by discussing various primary studies. They did not group the cognitive outcomes according to the type of domain.

The precious reviews also had their limitations with regards to study methodology. None of the earlier reviews systematically searched the electronic databases available to include studies. Additionally there were also various methodological inconsistencies in the search strategy utilized. For instance, two of the reviews (Biringer et al., 2009; Francomano et al., 2011) which were carried within a timeframe of 2 years had only one primary study in common between them. Also there was a lack in transparency with regards to reporting selection criteria and search procedures. No quality assessment of the available evidence from the included studies was done by any of the previous reviews.

In addition, most of the past studies except Biringer et al., 2009 and Francomano et al., 2011 had few numbers of second-generation antidepressants studies in them.

Problem Statement

Why study the effects of second-generation antidepressants on cognition?

Antidepressants along with their primary use in depression are also used in anxiety, panic disorder, OCD, ADHD and other mental disorders. However the focus of this study was on depression as antidepressants are primarily indicated for treating depression, and cognition dysfunction is an important issue and one of the primary diagnostic symptoms for depression according to DSM/ICD criteria.

Second-generation antidepressants are currently the first-line of treatment for depression and hence identifying specific antidepressants/ antidepressant classes which improve cognition may help the drug selection process and guide physician prescribing practices for depressed patients with existing cognitive impairments and may help in speeding functional recovery (Greer et al., 2010).

The majority of the depressed population is treated in an outpatient setting and expects to continue with their professional life and routine during the treatment. Experiencing cognitive impairment can not only threaten the performance of activities of daily living but also antidepressant treatment compliance. Hence it is essential that prescription of antidepressants minimally impair cognition (Amado-Boccara et al., 1995).

Trivedi et al., 2014 conclude the presence of mixed results regarding the ability for antidepressant treatment to improve cognitive performance in MDD and has concluded that studying the effects of antidepressant on cognitive

impairment in MDD should be a focus of upcoming studies. No study till date has been carried out which has systematically reviewed the literature and conducted a meta-analysis to combine and quantify the evidence present in the scientific literature.

CHAPTER 2

LITERATURE REVIEW

This chapter reviews the existing literature reviews which have previously evaluated the effects of antidepressants on cognitive functions based on the primary literature. Four reviews that examined cognitive effects of antidepressants were found. In addition to details of each study, a brief summary of the findings was reported at the end of the chapter.

Knegtering et al., 1994 conducted a narrative literature review to summarize the effects of antidepressants on cognitive function in the elderly (≥60 yrs.). Medline (1981-1993), former review articles and references from other studies were searched using the terms *antidepressant, cognitive functions, human performance,* and *cognitive performance.* The review was inclusive in its approach with respect to inclusion of various types of study designs such as of case control, crossover, placebo controlled, fixed dose, and single/ double blind studies. The evidence table reported the number of study participants, study design, duration of study, type and dose of antidepressants and the test used to diagnose cognitive function. The review consisted of 6 studies (n=88) on elderly healthy volunteers and 12 studies (n=468) on elderly patients with depression. The review concluded that MAO inhibitors minimally affect cognitive performance; SSRIs had no damaging influence on cognition; TCAs (Amitriptyline, Dothiepin) & Heterocyclics (Mianserin,Trazodone) impair attention/concentration – attributed to their sedative properties; drugs with anticholinergic properties e.g. Amitriptyline, Nortriptyline and Maprotiline impair

memory and in case of Nortriptyline, increased plasma concentration led to an increase in cognitive impairment. Also, deleterious effects of antidepressants might be disguised by improvements of affective state and that the initial adverse effects of antidepressants might not improve as a consequence of continued treatment. The strength of the study consisted in categorizing primary studies obtained into – studies on elderly healthy volunteers and studies on elderly patients with depression to analyze and highlight the difference due to existing depressive states on cognition. Although this study was one of the first to report and examine this area, it was a traditional literature review in which the study findings were not converted to a single metric and analyzed as a weighted average estimate of the evidence, i.e. a meta-analysis. It did not systematically search all the available electronic databases. There was also no description of study eligibility criteria, and no quality assessment of the included primary studies was done. Finally, at the time the review was done, TCAs were a frequently used category of the drug class. Hence, it focused more on TCAs and less on newer drugs classes like SSRI.

Boccara et al., 1995 reviewed and synthesized information about differential effects of antidepressants on cognitive function to facilitate appropriate prescription of these drugs. This study was also a narrative literature review that examined evidence from both observational and randomized control trials. Study design, duration of the study, type and dose of antidepressants, neuropsychological test used were some of the variables that were extracted and studied. The review concluded that familiarization with the test used to detect

cognition can mask real cognitive impact of pharmacotherapy. The review found that, in single dose studies, cognitive impairment was observed in antidepressants with strong anticholinergic or sedative effect. Also, long-term use of anti-depressants in depressive patients led to harmonization of cognitive function along with improvement in mood. Also alcohol was seen to enhance the effect of sedative antidepressants but there were no negative effects seen on other drugs. It also highlighted that antidepressants with sedative or anticholinergic action should be cautiously prescribed in the geriatric population as their prior cognitive functioning may be uncertain. The strength of this review was in the domain specific analysis carried out thorough contrasting cognitive effects of antidepressants at various treatment/patient/administration levels: antidepressants with sedative impact, antidepressants with no cognitive effect and antidepressants with positive cognitive effect - each analyzed for single versus repeated administration and in healthy versus depressed subjects. The limitations were similar to that of Knegtering et al., 1994 which included lack of predefined selection criteria, no systematic search of the available electronic databases, and no quality assessment of the included primary studies along with poor presence of evidence for SGADs.

The study done by **Biringer et al., 2009** examined and reviewed the literature on modern antidepressants effects on neurocognitive function. Medline, EMBASE and PsycINFO were searched. Like the previous reviews, this was a narrative literature review which did not carry out a systematic review and meta-analysis. This review focused its efforts mainly on analyzing the evidence from

double-blind, randomized studies and extracted patient sample size, study design, duration of the study, age of the participants, antidepressant type, type of cognitive impairment and neuropsychological test used as key parameters. The review concluded that SSRIs generally did not affect cognitive function. However, Paroxetine was associated with decreased performance on tests. Sertraline was found to be better than other SSRIs with respect to cognitive function. Additionally, Reboxetine, Bupropion and SNRIs were found to be better than other antidepressants and should be the drugs of choice in treating patients with depression who had the risk of cognitive impairment. The review also reported a lack of studies assessing effects of RIMAs and α2-receptor antagonists on cognitive function. The strength of this review lies in its within and between group analyses of antidepressants. Moreover being a relatively recent review it included many primary studies on modern antidepressants in it. Similar to previous reviews, this study did not specify study selection criteria and quality assessment was not conducted.

The study by **Francomano et al., 2011** is the most recent available evidence on the impact of antidepressant treatment on cognitive performance. The review was prompted by the numerous clinical observations of the effects of cognitive impairments on the quality of life in depressed patients. Unlike previous reviews, it had a predefined set of screening criteria for the inclusion of primary studies. The inclusion criteria consisted of primary studies that were in the English language consisted of trials with adult patient samples (age≥18) with n>30, diagnosis of psychiatric disorder established through DSM diagnostic

criteria, used neuropsychological tests to estimate cognitive functions and used MADRS or HDRS to assess affective disorders. The review searched PubMed and PsycINFO databases from (2006 – 2011) with *Major depressive disorder (MDD), cognition, neuropsychology* and *antidepressants* as key search terms. This narrative literature review consisted of 15 primary studies included (-5 non-blinded clinical trials, 6 case control studies, 3 double-blind controlled clinical trials and 1 prospective partially randomized trial. Sample size, study design, duration of the study, type and dose of antidepressants, test used, type of cognitive impairment and neuropsychological test used were some of the parameters extracted from the primary studies. This review concluded that depression may subside with antidepressant therapy, but cognitive deficits may persist. Also, cognitive impairment associated with the use of antidepressants is frequently reported during the acute phase of the illness. Proper and prompt treatment with SSRIs & SNRIs may protect against cognitive impairment, especially visual and verbal memory. This effect (found greater for SNRIs) lingers even after stopping the treatment during recovery. However, the aforementioned evidence did not sustain when carried out in depressed patients which. It also attributes the higher prevalence of cognitive deficits in elderly to aging and presence of cardiovascular and cerebrovascular comorbidities. It raises the difficult question of whether cognitive improvement in depression is due to the antidepressant treatment or due to encouraging prognosis. Similar to earlier reviews, this review did not perform a meta-analysis, quality assessment or a domain specific analysis with respect to cognition or antidepressant type.

Summary of Existing Literature

Overall, four reviews were found to be of similar objective to that of our study goals. Although previous reviews that had synthesized the evidence of the effects of antidepressant on cognitive function had been carried out, nearly all of them were narrative reviews which had just theoretically discussed the various aspects of cognitive effects of antidepressant therapy. None of these studies were carried out in a systematic manner or were able to conduct a meta-analysis to combine and quantify the evidence present in the scientific literature.

A comprehensive database search of the scientific databases was also not carried out. Additionally there were various methodological inconsistencies in the search strategy utilized. For instance, two of the reviews (Biringer et al., 2009; Francomano et al., 2011) that were carried within a timeframe of 2 years had only one primary study in common between them. Also, there was a lack in transparency with regards to reporting selection criteria and search procedures. In addition, no quality assessment of the available evidence was done by any of the previous reviews.

This study is a systematic review of body of literature based on the scientific databases like Medline, PubMed, PsycINFO, CINAHL and EMBASE. It was designed to analyze the available evidence and combine it quantitatively by performing a meta-analysis. The study has strict inclusion and exclusion criteria along with the use of quality assessment scale to screen and select the most

rigorous and strong evidence i.e. primary studies, obtained for our systematic review. Also a domain specific analysis with regards to antidepressant classes, and type of cognitive impairment was planned based on the availability of the data.

CHAPTER 3

METHODS

This chapter includes the methodology used to estimate and quantify the effects of second-generation antidepressants on cognition through a systematic review and meta-analysis based on the most recent scientific literature. Specifically, the details of data source, study selection criteria, and data management and analysis are described. This study has been reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis: The PRISMA Statement (Liberati et al., 2009).

Research Question

The PICOS is a taxonomy used in evidence-based medicine to formulate research questions with respect to Patient Population, Intervention, Comparator, Outcomes, and Study Design. It helps in developing a concise statement of work with key points that are easy to understand and highly translatable.

P (Patient population) – The patient population included adults of all ages suffering from depression who had taken antidepressants in any clinical setting along with studies conducted in all countries.

I (Intervention) – The intervention included second-generation antidepressants marketed in the United States based on the American Hospital Formulary Service (AHFS) 2014 drug classification.

C (Comparator) – The comparators included placebo or second-generation antidepressants. Studies involving first-generation antidepressants were excluded.

O (Outcomes) – Cognitive functions evaluated, included any: impairment/improvement in attention, memory, mental processing speed, language processing, psychomotor performance and executive functions.

S (Study design) – Both Randomized Controlled Trials (RCTs) and observational studies were included to examine the effect of an antidepressant on cognitive functioning. A quality checklist was used to grade and screen the studies to ensure consistency and transparency. Reviews, case reports and incomplete interviews were excluded.

Methods

Data sources and search strategies

Literature search was conducted in Medline, PubMed, PsycINFO, EMBASE, and CINAHL from January 1980 to May 2014 to identify studies eligible for this meta-analysis and systematic review.

MEDLINE® is U.S. NLM's premier bibliographic database that has over 21 million references to life sciences journal articles (from 5,600 worldwide journals in about 40 languages) with a focus on biomedicine and health. A unique feature of MEDLINE is that indexes records using the NLM Medical Subject Headings (MeSH®). It covers time periods from 1946 to present along with some older material. MEDLINE mainly covers scholarly articles, but also includes few

newspapers, magazines, and newsletters (MEDLINE Fact Sheet). Ovid, a service that provides access to MEDLINE data, was used.

PubMed is a free resource established and maintained by the National Center for Biotechnology Information (NCBI) at the National Library of Medicine® (NLM). It allows free access to Medline in addition to in-process citations that are yet to be added to Medline (PubMed Fact Sheet).

PsycINFO® is database produced by American Psychological Association (APA) dedicated to literature in behavioral sciences and mental health. It has more than 3.7 million records from over 2500 journals along with books and dissertations. It is based on Thesaurus of Psychological Index Terms (APA 2014).

Cumulative Index of Nursing and Allied Health Literature **(CINAHL Plus with Full Text)** is the most comprehensive and largest nursing and allied health (alternative/complementary medicine, biomedicine, consumer health, health sciences librarianship etc.) research database dating back to 1937. It also includes Evidence-Based Care Sheets and Quick Lessons which provide a succinct overview of various diseases and conditions and summarizes the most effective therapeutic options. CINAHL Subject Headings follows MeSH structure used by NLM (EBSCO Host 2014).

Embase® is a biomedical database from Elsevier. It contains millions of articles from more than 7,000 journal titles. Although there is around 60% overlap of the covered journals with MEDLINE, 40% are unique to Embase, particularly in

the area of drugs/ pharmacology from European literature. The indexing is based on the Emtree thesaurus, which has over 56,000 terms (VU Embase 2013).

The year 1980, date of the DSM-III publication, was used as a cut off in order to reduce diagnostic heterogeneity (Tedeschini et al., 2011; Calati et al., 2013). Also, most of the second-generation antidepressant approved for clinical use was introduced in the 1980s and hence the search timeline was started from 1980 to capture all the relevant studies. The search concepts used were: depression (inherent study population attribute concept), cognitive function (primary outcome concept) and antidepressants (intervention concept). The following keywords were used: depression, cognition, cognitive function, adverse event, side effects, antidepressant and the name of each antidepressant active compound together with cognition or other keywords. The search was limited to human subjects and English language only. Reference lists from identified articles and reviews were used to find additional articles. An experienced University of Texas Health Science Center librarian and search specialist was consulted to plan search strategies for the different electronic databases in order to obtain a comprehensive inventory of available studies. Each electronic database by the virtue of its idiosyncratic controlled vocabulary required a different approach to searching and appropriate terms. A detailed description of the search strategies used is shown in Appendix A.

Study Selection (Eligibility Criteria)

To be included, *a priori* selection criteria were developed.

(i) The studies that aimed at estimating the effect of antidepressants on cognitive function were included. Studies that addressed a different research question such as measuring efficacy/or adverse event of antidepressants, but that included estimates for cognitive impairment/improvement were also considered.

ii) The study population should have a diagnosis of depression based on the depression diagnostic instruments either administered by clinicians or researchers or self-administered by participant. It included criteria for Major Depressive Disorder (MDD) or dysthymic disorder or depression, according to the International Classification of Diseases (ICD-9 or ICD-10) or the Diagnostic and Statistical Manual of Mental Disorders (DSM-III, DSM-III-R, DSM-IV or DSM-IV-TR).

iii) All the study participants were aged 18 or older.

iv) Only primary studies of both RCT and observational nature were included in the study; abstracts, reviews, case reports, case series, dissertations, systematic reviews and meta-analyses were excluded. Duplicate publications were excluded.

v) Only studies in the English language were included.

vi) Studies involving non-human subjects were excluded

vii) The operational definition of antidepressants was based on second-generation antidepressants) marketed in the US classified under American Hospital Formulary Service® Drug Information 2014 (AHFS DI) drug

classification categories from the American Society of Health-System Pharmacists (ASHP). Studies employing herbal preparations e.g. St. John's Wort, electroconvulsive therapy, or psychotherapies were excluded unless they had an active second-generation antidepressants or placebo comparator present.

viii) The studies should have a control group which is also depressed so that the causal effect of second-generation antidepressants on cognitive function could be found.

ix) Studies that had sufficient data to calculate effect size and standard error were included. For instance, studies reporting cognitive changes graphically without providing numerical values for them were excluded.

x) Due to wide variation in measuring cognitive function in different cognitive domains, an inclusive approach with regards to neuropsychological tests was used.

xi) If the quality assessment suggested low quality of the study, it was excluded.

xii) Studies from all countries of the world were eligible.

xiii) Studies that had patient reported outcomes for measuring cognitive change were only included. Studies that provided imaging as a measure for a change in cognition was not considered.

xiv) Studies should have been published between 1980 and 2014 only.

Coding of Exclusion criteria

The following coding scheme (Table 2.) was used to exclude studies based on the – Population, – Intervention, – Comparator, – Outcome, – Methodology, – Publication Date, – Language, and – Insufficient Data.

Table 2. Coding of exclusion criteria used for screening

Criterion	Include if	Exclude if	Action
Population	Adults (age≥18) of all ages suffering from definite diagnosis of depression who had taken second-generation antidepressants in any clinical setting in any country were eligible. Study population age is unclear	Population aged <18 years; non-human subjects	If population is wrong, mark the study POPULATION Otherwise move to next criterion
Intervention	Second-generation antidepressants (SGAD) marketed in the United States classified under AHFS 2014 drug classification categories	Study does not include SGAD drug therapy	If the intervention is not appropriate, mark the study INTERVENTION Otherwise move to next criterion
Comparators	second-generation antidepressants, other drug therapy	Study has no comparator arm	If the comparators are not present/appropriate, mark the

	non-drug therapy, placebo, usual care along with second-generation antidepressants or no treatment		study COMPARATOR Otherwise move to the next criterion
Outcomes	Relevant outcomes include impairment/improvement in attention, memory, processing speed, and executive functions. Do not exclude on outcomes, but article must report data on at least one clinically-relevant cognitive outcome.	Article does not report any clinically-relevant cognitive outcomes of interest	If the article does not report any relevant outcomes, mark it OUTCOME Otherwise move to the next criterion
Study design	Randomized controlled trials and observational studies	Other study methodology which includes abstracts, case studies/reports, commentaries, expert opinions, dissertations, letters, book chapters,	If the study methodology is inappropriate, mark it METHODOLOGY Otherwise move to the next criterion

		guidelines, retractions and SR/MA. Also duplicate/redundant studies	
Language	English-language publications only	Foreign-language publication	If the full text article is not published in English, mark it LANGUAGE Otherwise move to the next criterion
Incomplete Data	Sufficient data is included in the study to calculate effect size and standard error for further Meta-analysis	Incomplete / insufficient/ partial data	If the study has insufficient data, mark it INSUFFICIENT DATA If the study meets all criteria, mark it MAYBE

Data management and Screening

Refworks (ProQuest), a web based citation management tool was used to store and check for duplicates within the citations obtained from the database searches previously conducted. After the removal of duplicate studies, the titles and abstracts of each citation from Refworks were imported into Excel workbook specially designed to screen titles and abstracts for this review

The primary author screened titles and abstracts, according to pre-specified selection criteria, blinded to author name and journal, in Excel workbook to record inclusion decisions as either "no" and then the primary reason for "no" chosen from the exclusion criteria dropdown options or "maybe". For those citations that were classified as "maybe" and for those where eligibility could not be assessed based on title and abstract alone, the full text was obtained for final consideration and then the maybe's were recorded as either "no" plus the main reason for it or a "yes".

To ensure reliability of screening of abstracts, 66 abstract were screened independently by another author. The Cohen's Kappa for Inter-rater reliability was found to be 1.00. In the case of disagreements between the 2 coders, discussions and review of the differential abstraction was done until they agreed or a third author was consulted to serve as an arbitrator.

Data Extraction and Synthesis

The data extraction for the included studies (“yes” ones) was conducted by the primary author. Information for the following constructs was coded (Appendix B): Citation information, study-level information (type of study, location, setting, sample size and demographic characteristics), measures of cognitive function (type and measuring instrument), depression and treatment measures (depression instrument used to diagnose, severity of depression, family and past history, name, dose, and duration of administration of the drug).In addition to the descriptive information, all data needed for the statistical analysis, including numerical change in cognitive domains measured by tests, relative 95 % confidence intervals (95%CI), standard error (SE), or p value for each exposed group (or data useful to derive such estimates), were extracted from published studies. Detailed information regarding the variable coding is provided in the code book. The data extraction form was pilot tested on 3 studies for comprehensiveness and ease of interpretability. The data extraction elements were in concordance with the CONSORT (Moher et al., 2010) and STROBE (Von Elm et al., 2007) statements that provide the guidelines for reporting randomized trials and observational studies, respectively.

Study Quality Assessment

The quality of evidence pertaining to randomized clinical studies was assessed using Cochrane risk of bias tool for RCTs (Appendix C). Sequence

generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data and selective outcome reporting were assessed, and each of them was graded as "yes (+)", "no (-)" or "unclear (?)", which indicated low risk of bias, high risk of bias and uncertain risk of bias, respectively. Conflicts in assigning quality assessment grades were resolved by discussion or the consultation of a third reviewer. No observational study was selected; consequently, no quality assessments for them were made.

Data Analysis

The main outcome of interest in this study was change in test score for each cognitive domain. The outcome was measured among individuals with depression who were being treated with antidepressants. A random effects model was used to estimate the pooled effects of antidepressant use on cognitive functioning as there exists variation in effect size due to heterogeneity of study settings, populations, and timeline. The random effects model provides combined mean effect size for studies that provided a random distribution of effect sizes. This method represents a more conservative approach compared with a fixed effect model.

Forest plots

They are commonly used to graphically display the results of a meta-analysis. The plots include the study name and Refworks identification number, the outcome – along with means, p-value, and visual display of standard

difference in means and confidence interval, and relative weight. The standardized mean difference is a summary statistic and indicates the size of the intervention effect in each study corresponding to the variability observed in that study (Cochrane Handbook, 2011).

In the graphical display of the study results, the line in the middle is known as 'the line of no effect' which has the value of 0 when the outcome is continuous in nature (Ried, 2006). The boxes positioned on the horizontal lines denote the effect estimates for individual studies. The size of the box is directly associated with the contribution to the meta-analysis by the weight of the study. The horizontal lines (whiskers of the confidence interval) represent the length of confidence interval for each study. The length of the line is directly proportional to the width of the confidence interval and indirectly proportional to the precision of the study results. The relative weight column shows the influence and contribution of the individual study on the ultimate result of the meta-analysis. The relative weight is directly proportional to the size of the box and the influence of the study on the result. The study's sample size and precision of its result provided by the confidence interval, determine the weight of the study. Thus larger the study sample size and narrower its confidence interval, the more weight the study has in the meta-analysis (Ried, 2006).The diamond depicted in the last row of the Forest plot illustrates the net result of the meta-analysis. The center and width of the diamond denotes the overall effect estimate and overall confidence interval respectively.

Heterogeneity

It is defined as inconsistency in the treatment effect across the included studies (Deeks et al., 2001). Studies included in a meta-analysis vary and testing for heterogeneity helps in measuring this variability between studies. Heterogeneity statistics indicates the comparability of the studies included in the meta-analysis (Ried, 2006). Pooling data from multiple trials in the presence of substantial heterogeneity and presenting a single net estimate can be specious (Thompson and Pocock, 1991).

I^2 testing quantifies heterogeneity of the selected studies (Higgins and Thompson, 2002; Higgins et al., 2003). The I^2 statistic describes the percentage of the total variation across studies brought about by heterogeneity rather than by chance (Higgins et al., 2003). Threshold for the interpretation of the I^2 statistic are as follows:

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity*
- 50% to 90%: may represent substantial heterogeneity*
- 75% to 100%: considerable heterogeneity*

The importance of the observed I^2 values should be interpreted depending on (i) effect direction and magnitude and (ii) strength of proof for heterogeneity (e.g. P value from the χ^2 test, or CI for I^2) (Cochrane Handbook, 2011). In this research, the presence of heterogeneity was assessed using the I^2 statistics. The values for I^2 statistic were categorized as either small (from 25% to <50%),

medium (from 50% to <75%) or large (≥75%). Non-overlapping CIs were considered statistically significant.

Publication bias

Publication bias refers to the greater probability of studies that report positive findings to get published (Begg and Berlin, 1989; Easterbrook et al., 1991; Dickersin and Min, 1993; Stern and Simes, 1997; Egger and Smith, 1998). Studies with findings that are not statistically significant are less likely to get reported or published due to the tendency of the editors and reviewers to publish studies with positive results that support the hypothesis of the researcher. (Decullier et al., 2005; Dwan et al., 2008; Lee et al., 2008; Song et al., 2009; Turner et al., 2008). This leads to studies with negative results mot getting published or even not getting submitted for publication (Zlowodzki et al., 2007). A ramification of such research underreporting is its effect on the sample of studies that get available for conducting a meta-analysis and the resulting uncertainty regarding the validity of the results (Ahmed et al., 2012; Kirkham et al., 2010; Kicinski et al., 2013). For instance, inclusion of more studies that report a positive finding can result in overestimation of the treatment effect and may lead to a false-positive result (Zlowodzki et al., 2007).

The common methods for detection of Publication bias are: Funnel plot display to provide visual interpretation of the bias and statistical methods like Egger regression, and Duval and Tweedie's trim and fill.

Funnel plot

It consists of two types, one that plots a study's effect size against its standard error and the traditional form, which plots effect size against precision, the inverse of standard error). The increase in the sample size of the study leads to increase in precision (smaller confidence intervals) resulting in the true mean value in the population to be more likely represented by the point estimate of the outcome (Zlowodzki et al., 2007). Thus larger studies are seen towards the top of the graph and have a tendency to cluster near the mean effect size (CMA Manual). Owing to more random variation, smaller studies are peripherally dispersed and appear towards the bottom of the graph. The absence of publication bias is indicated by a plot that is symmetrically distributed and resembles an inverted funnel with its base at the bottom which assures that no studies have been omitted. In contrast, presence of bias leads to a higher concentration of studies on one side of the mean resulting in asymmetry at the base (CMA Manual).

DUVAL AND TWEEDIE'S Trim and fill

It is used to calculate the combined effect with adjustment of publication bias. It builds on the central notion underlying the funnel plot; that the absence of bias will result in a plot that should be symmetric around the summary effect. If more small studies are present on the right than on the left, then there could be studies missing from the left. The Trim and Fill procedure attributes these missing studies, tallies them to the analysis, and then re-calculates the summary effect size (CMA Manual).

EGGER'S LINEAR regression method

It quantifies the bias represented by the funnel plot. Unlike Begg and Mazumdar's test which utilizes ranks, Egger's method uses the real values of effect sizes and their precision.

In this study, Egger's regression test and Trim and Fill method were used to examine for the presence of potential publication bias along with analysis of funnel plots. For Egger's regression test, the alpha value for statistical significance was set at ≤0.05. All analyses including graphs were performed using Comprehensive Meta-Analysis, v2.2 (Biostat, Englewood, NJ)

CHAPTER 4

RESULTS

This chapter provides a summary of the primary studies selected after the application of the search strategy described in the previous chapter. Specifically, it also includes the results of the systematic review and meta-analysis of selected primary studies to estimate and quantify the effects of second-generation antidepressants on cognition.

Study Selection

After the electronic databases searches were carried out (Table 3.), a total of 6,659 records were obtained. These were then screened to remove internal and external duplicates which may occur due to overlapping of electronic databases as well as repetition within the databases.

Table 3. Primary studies obtained from electronic database searches

Interface/Database	Items found	Internal Duplicates	External Duplicates	New
Ovid Medline®	1328	50	206	1072
NLM PubMed	1246	0	1080	166
Ovid PsycINFO®	1263	9	408	846
EBSCO CINAHL® (MEDLINE excluded)	64	1	6	57
Ovid Embase®	2758	11	614	2133

After the removal of duplicates, 4,274 abstracts were screened according to predefined selection criteria. The review of abstracts resulted in selection of 342 articles which were reviewed in full. The full review of the articles resulted in selection of 17 records to achieve the research objective. This process of identification of eligible studies is shown in Figure 2.

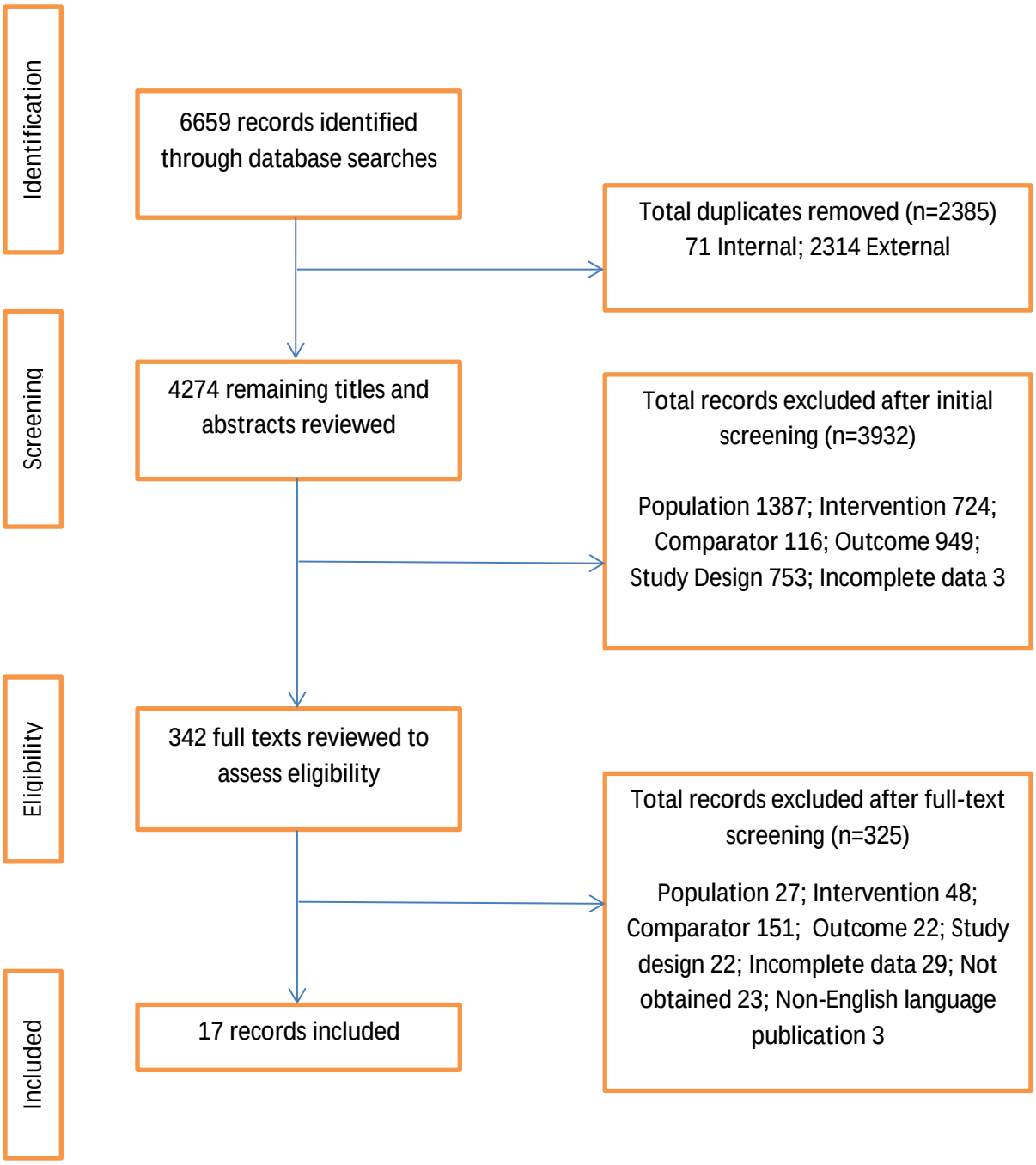

Figure 2. Identification of eligible studies

The table below (Table 4.) is evidence which briefly summarizes the studies which were deemed eligible for further analysis in our review.

Table 4. Demographic and clinical characteristics of the studies included in the meta-analysis

Refworks ID #	Author, Year, Country, Funding source	Study Design	Depression Care setting	N, Depression type , Mean Age, Gender (F%), Comorbidities present, Comedications used	Treatment group Antidepressant / Daily dose (mg)	Control group tx	Follow-up time
485	Strik et al 2006, The Netherlands ; Industry	RCT	University Hospital	54 post first-time MI depression; (age between 18 and 75 years); 56.4 yrs.; 29.6%; MI; various cardiovascular drugs	fluoxetine 20 mg (N=27) increased up to 60 mg depending on clinical response	placebo (N=27)	9 weeks
703	Rocca et al 2005; Italy; None	Obs.	University Psychiatric section - Outpatient	138 minor depressive disorder or subsyndromal depressive symptomatology; (≥65 yrs. old) 72.15 yrs.	escitalopram 20 mg (N=66)	sertraline 50 mg (N=72)	1 year
1022	Geretsegger et al 1994; Austria + Germany; Industry	RCT	Inpatient + Outpatient	106 major depression; 74 yrs.; 86.79%	paroxetine 20 - 40 mg (N=54)	fluoxetine 20-60 mg (N=52)	6 weeks

1093	Robinson et al 2000; US+ Argentina; Mixed	RCT	Rehabilitation Hospital	27 post stroke depression; 69 yrs.; 35%	fluoxetine 10 mg (N=14) gradually increased to 40 mg	placebo (N=13)	12 weeks
2338	Munro et al 2012; US; Mixed	RCT	Outpatient memory clinics	131 depression of Alzheimer's disease; 77.3 yrs.; 54.05%; some patients tx with cholinesterase inhibitors and/or memantine	sertraline 100 mg (N=67)	placebo (N=64)	24 weeks
2389	Katona et al 2012; Multinational; Industry	RCT	Psychiatric, psychogeriatric and geriatric settings	448 recurrent major depressive disorder; 70.56 yrs.; 66.29%; Concomitant medications(≥ 5% of the patients) - simvastatin, aspirin, multivitamins and hydrochlorothiazide	vortioxetine 5 mg (N=155) duloxetine 60 mg (N=148) (reference)	placebo (N=145)	8 weeks
2652	Culang et al 2009; US; Mixed	RCT	University affiliated outpatient psychiatry clinics	174 non-psychotic unipolar depression community dwelling (75 years or older), 79.57 yrs.; 58%	citalopram 20 mg (N=84)	placebo (N=90)	8 weeks
2710	Herrera-Guzmán et al 2009; Mexico; Mixed	Obs.	Unspecified	73 major depressive disorder; 20-50 yrs. (33.06 yrs.); 80.8%	duloxetine 60 mg (N=37)	escitalopram 10 mg (N=36)	24 weeks
2775	Hoffman et al 2008; US; Mixed	RCT	Unspecified	98 major depressive disorder; Age ≥ 40 (51.5 yrs.); 76.54%	sertraline 50-200 mg (N=49)	placebo (N=49)	4 months

2933	Sato et al 2006; Japan; University Grant	Obs.	Inpatient - Hospital	18 major + minor post stroke depression (PSD) patients; 58.2 (41-75) yrs.; 27.8%; recently developed strokes; rehabilitation treatment	milnacipran 30-60 mg (N=10)	no anti-depressant (N=8)	3 months
3022	Lee et al 2005; South Korea; Unspecified	RCT	Hospital Trauma Center - inpatient + outpatient	20 MDD with mild to moderate degree of traumatic brain injury(TBI); 18-55 yrs. (34.55 yrs.); 20%	sertraline 25 mg (N=10) increased every 2 days until it reached 100 mg	placebo (N=10)	4 weeks
3055	Munro et al 2004; US; Government	RCT	Outpatient clinic	41 MDD + Alzheimer's disease; 77.55 yrs.; 68.29%	sertraline 25-150 mg (N=23)	placebo (N=18)	12 weeks
3097	Doraiswamy et al 2003; US; Industry	RCT	Outpatient	290 major depressive disorder 60 years of age or older (single episode or recurrent, without psychotic features); 67.7 yrs.; 56.5%	sertraline 50-100 mg (N=185)	fluoxetine 20-40 mg (N=105)	12 weeks
3593	McIntyre et al 2014 Multi-national ; Industry	RCT	Psychiatric inpatient and outpatient settings	598 recurrent MDD during a depressive episode of moderate severity or greater; (adults aged 18-65 yr.) Women (66.22%)	vortioxetine 10 mg (N=195) vortioxetine 20 mg (N=207)	placebo (N=196)	8 weeks

3910	Weintraub et al 2010; US; Mixed	12 week extn. efficacy trial after 12-week, RCT	Memory disorder clinics	131 depression of AD (dAD) mild-moderate dementia severity and a moderately depressed group; median age of 79 yrs.; 54%; concurrent cholinesterase inhibitor and memantine tx	sertraline 50-100 mg (N=67)	placebo (N=64)	24 weeks
4456	Ferguson et al 2003; US; Industry	RCT	Unspecified	49 MDD; (aged 18–65 years); Unspecified	paroxetine 20–40 mg (N=23) reboxetine 8–10 mg	placebo (N=26)	8 weeks
4842	Shah et al 2013; India; None	Obs.	Psychiatry outpatient department of Hospital	41 medication naïve patients with depression; age 18–50 years (30.97 yrs.); 34.14%	fluoxetine 20 mg (N=21) citalopram 20 mg (N=20)	imipramine 150 mg	12 weeks

Overview of the selected studies

The Cohen's Kappa for Inter-rater reliability was found to be 1 which indicates perfect agreement between the raters. The selected 17 studies (13 RCTs and 4 Observational) involved a total of 2,437 depressed patients. Most of the studies had a placebo comparator with only 5 studies having an active comparator. The study duration ranged from 4 weeks to 1 year. Study subjects comprised of adults of all ages with around half of the studies (n=9) having a sample mean age of greater than 65 years. Ten studies included more than 50% women. Studies were conducted in 20 countries: US (n=11), Germany (n=3), Mexico (n=2), Canada (n=2), Finland (n=2), France (n=2), Ukraine (n=2), Netherlands, Italy, Austria, Argentina, Australia, Latvia, Serbia, Slovakia, South Africa, Sweden, Japan, South Korea, and India. Across the 17 studies, participants were described as receiving either one of the following: Citalopram, Escitalopram, Fluoxetine, Paroxetine, Sertraline, Duloxetine, Milnacipram, and Vortioxetine. The effect of antidepressants on cognition was measured for each cognitive domain using 43 unique neurocognitive tests. The studies were sorted according to the cognitive tests' frequency (Appendix D) Mini-mental state exam (MMSE), Stroop Color Word test, Choice Reaction Time Task and Digit Symbol Substitution Test (DSST) were the most common tests (Table 5.) used across the studies which fulfilled the inclusion criteria (minimum of 3 studies per test per study design type for further systematic review and meta-analysis).

These studies were assessed by the Cochrane Risk of bias tool (Higgins, J. et al. 2011) and were found to be of optimum quality.

Table 5. Most common tests used across the studies

COGNITIVE ASSESSMENT TEST	COGNITIVE DOMAIN	STUDIES CONTAINED REFWORKS ID #		
		RCT	OBS.	TOTAL #
Mini-mental state exam (MMSE)	Global cognitive function	1022, 1093, 2338, 2652, 3022, 3055, 3097, 3910	703, 2933	10
Stroop Color-Word test	Executive function	485, 2652, 2775, 3593	2710	5
Choice reaction time task	Attention, processing speed	2652, 3022, 3593, 4456	None	4
Digit Symbol Substitution Test WAIS-III	Attention, processing speed	2389, 2652, 3593	None	3

Meta-Analysis of Studies involving Mini?mental state examination (MMSE)

The MMSE is a brief 30-point questionnaire which measures global cognitive impairment. It comprises of items which check for arithmetic, memory and orientation. Scoring ranges from 0-30 with higher scores indicating better performance (Folstein et al., 1975). There were eight RCTs that evaluated the effect of second-generation agents by MMSE (Table 6.). Studies with Refworks Id. # 1022 and 3097 were excluded from the meta-analysis as they lacked a placebo comparator.

Table 6. Studies included under MMSE test

RefWorks Id #	Author/ Year	Treatment group	Comparator group
1093	Robinson et al., 2000	Fluoxetine	Placebo
2338	Munro et al., 2012	Sertraline	Placebo
2652	Culang et al., 2009	Citalopram	Placebo
3022	Lee et al., 2005	Sertraline	Placebo
3055	Munro et al., 2004	Sertraline	Placebo
3910	Weintraub et al., 2010	Sertraline	Placebo

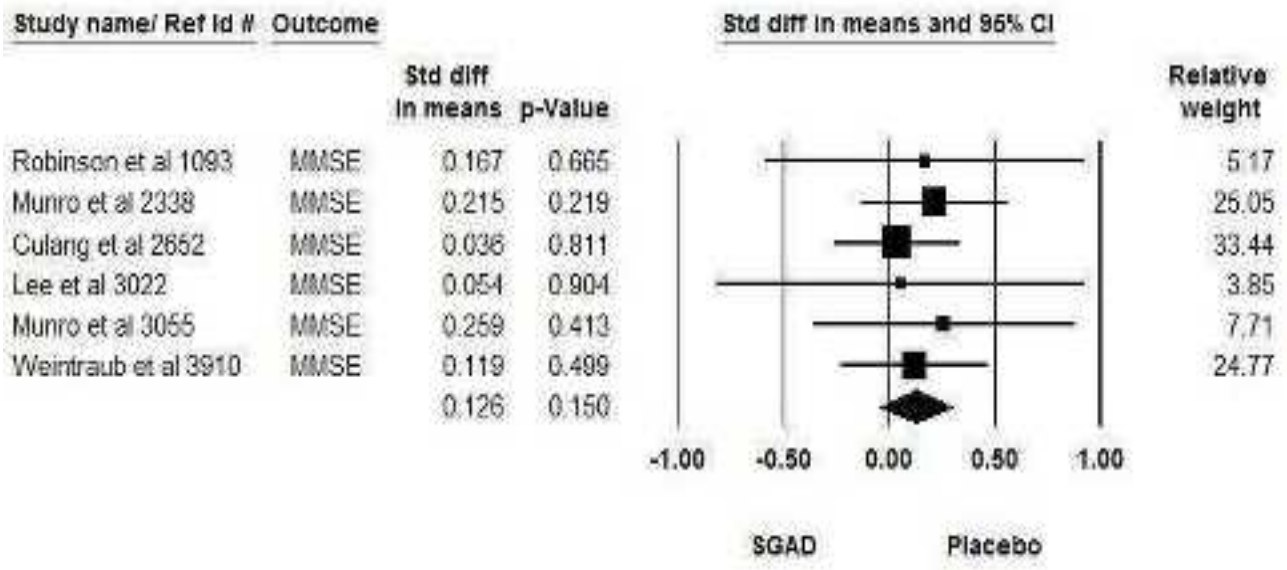

Figure 3. Forest plot for MMSE studies (I2=0%, p= 0.975)

Six studies were found eligible for inclusion into the meta-analysis for MMSE (Figure 3.). The $p > 0.05$ and the diamond having the' line of no effect' in its confidence interval shows that the results we not significant. Thus there is no difference in the effect of SGADs and placebo on MMSE that measures global cognition.

Test for Heterogeneity

Testing the heterogeneity for the MMSE meta-analysis revealed overlapping confidence intervals of the individual studies and an I^2 value of 0% along with a non-significant p-value (0.975). The tests suggest that the studies included in the meta-analysis as homogenous.

Publication bias

When there are fewer than ten studies in a meta-analysis, the test for funnel plot asymmetry (Figure 4. and Figure 5.) should not be used because the test power is generally too low to discriminate chance from real asymmetry (Sterne et al., 2011). Hence no conclusions were made from the funnel plots and further statistical analyses were conducted.

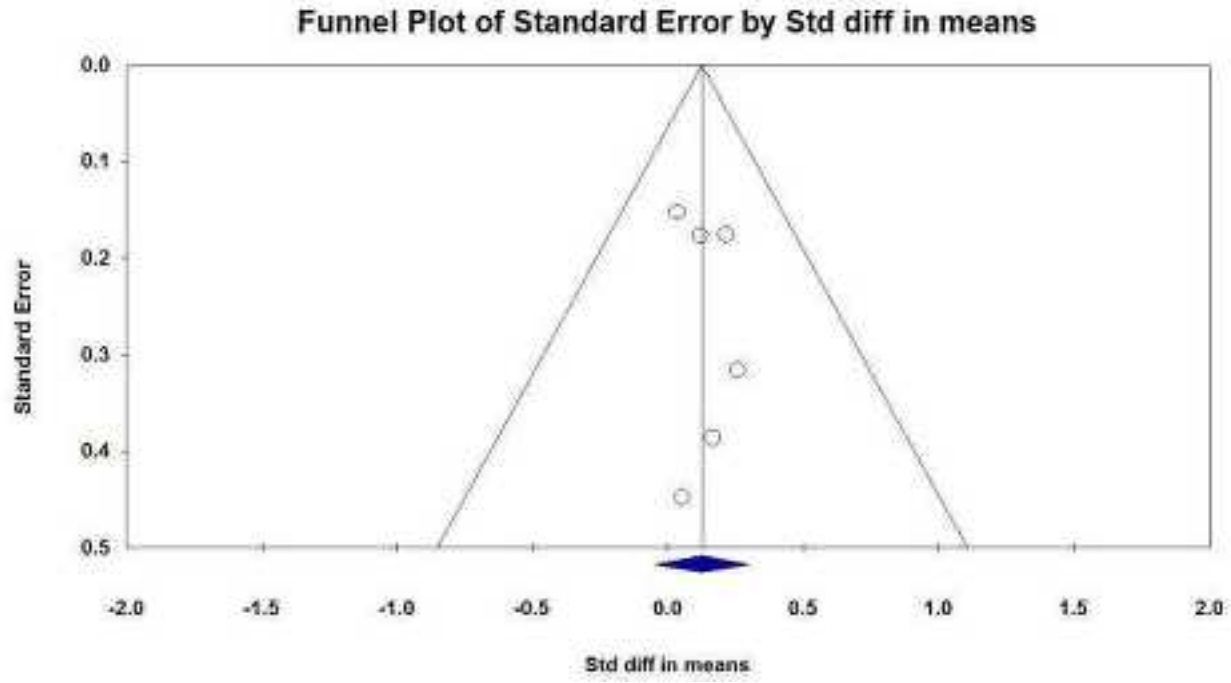

Figure 4. Funnel Plot of Standard error by Standard difference in means

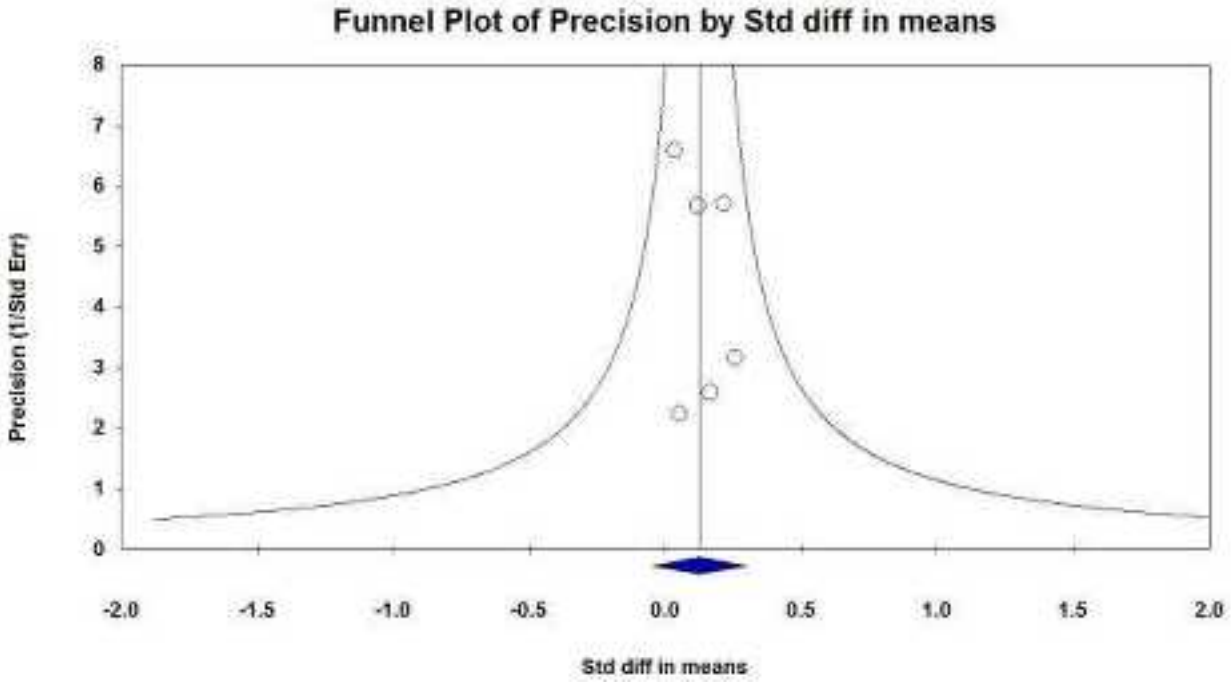

Figure 5. Funnel Plot of Precision by Standard difference in means

For the MMSE analysis there was one missing study. The data point for one imputed study is highlighted in black. (Figure 6.) In the fixed effect model, the estimate was 0.12627 (-0.04570, 0.29825). Using Trim and Fill the imputed point estimate is 0.11521 (-0.05050, 0.28091). Under the random effects model the point estimate and 95% confidence interval for the combined studies is 0.12627 (-0.04570, 0.29825). Using Trim and Fill the imputed point estimate is 0.11521 (-0.05050, 0.28091).

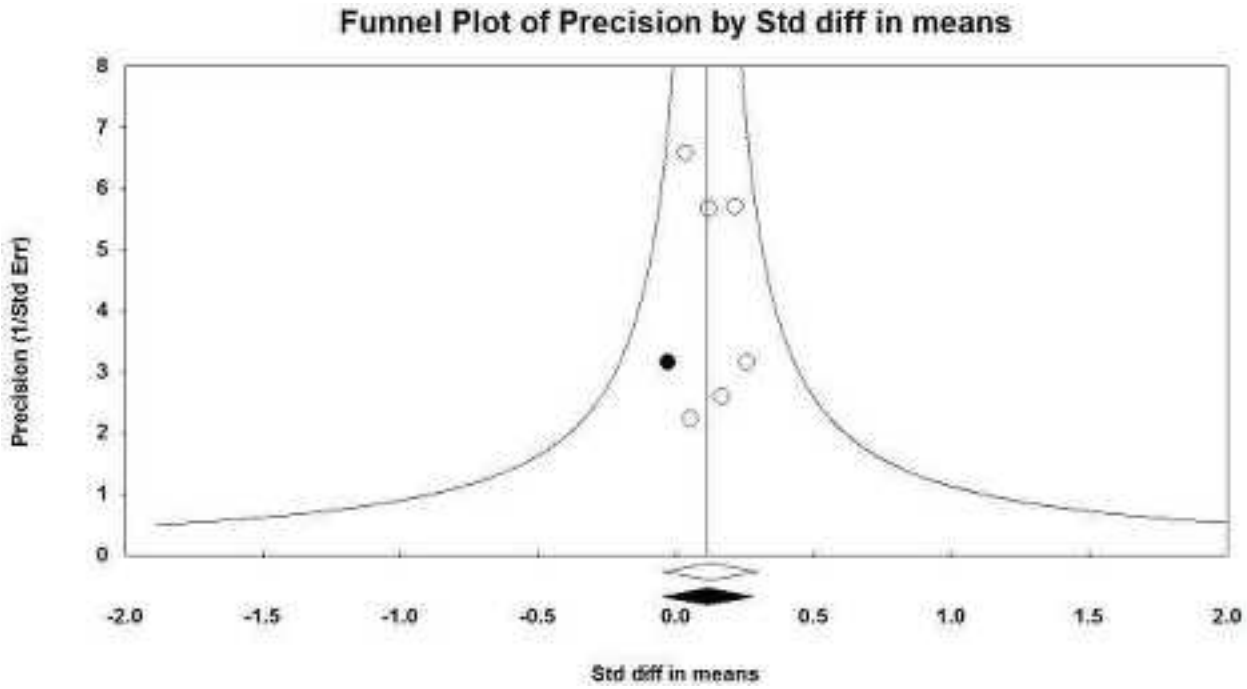

Figure 6. Imputed Funnel Plot of Precision by Log odds ratio

The Egger's method revealed that the intercept (B_0) was 0.29359, 95% confidence interval (-1.04627, 1.63344), with t=0.60837, DF=4. The one-tailed p-value is 0.28790, and the two-tailed p-value is 0.57579. The findings suggest that there is no significant presence of bias.

Systematic Review of Studies involving Stroop Color-Word Test (SCWT)

The SCWT assesses cognitive flexibility, resistance to interference from external stimuli and creative ability (Golden, 1978). It is based on the observation that individuals can read words relatively quicker than they can recognize and name colors. Test-takers have to read colored words or name the ink colors from different pages as quickly as possible within the time limit. Lesser the time taken for completion better is the cognitive outcome. There were four studies that evaluated the effect of second-generation agents by SCWT (Table 7.).

Table 7. Studies included under SCWT test

RefWorks Id #	Author/ Year	Treatment group	Comparator group
485	Strik et al., 2006	Fluoxetine	Placebo
2652	Culang et al., 2009	Citalopram	Placebo
2775	Hoffman et al., 2008	Sertraline	Placebo
3593	McIntyre et al., 2014	Vortioxetine	Placebo

The outcome for SCWT was modified and reported in different formats which prevented us from conducting a meta-analysis; hence, a systematic review was carried out. Although 4 studies were obtained, only 2 were used for carrying out the systematic review. Strik et al., 2006 found no differences in executive performance between depressed patients treated with fluoxetine or placebo. Culang et al., 2009 did not report whether the change in the test scores due to

SGAD treatment were statistically significant. Finally, Hoffman et al., 2008 and McIntyre et al., 2014 reported that sertraline and vortioxetine significantly improved executive performance in depressed patients compared to placebo.

Systematic Review of Studies involving Choice Reaction time task (CRT)

The CRT assesses the overall sensory-motor performance by measuring the ability to attend and respond to a stimulus (Hindmarch et al., 1977). The testing comprises of presenting either the word 'No' or the word 'Yes' on the monitor and then instructing the patient to press the corresponding button as quickly as possible. There were four studies that evaluated the effect of second-generation agents by CRT (Table 8.).

Table 8. Studies included under CRT test

RefWorks Id #	Author/ Year	Treatment group	Comparator group
2652	Culang et al., 2009	Citalopram	Placebo
3022	Lee et al., 2005	Sertraline	Placebo
3593	McIntyre et al., 2014	Vortioxetine	Placebo
4456	Ferguson et al., 2003	Paroxetine	Placebo

The CRT was modified by Lee et al., 2005 and Ferguson et al., 2003. which prevented us from conducting a meta-analysis. Hence a systematic review

was carried out. Although 4 studies were obtained, only 2 were used for carrying out the systematic review. Culang et al., 2009 did not report whether the change in the test scores due to citalopram treatment were statistically significant. Lee et al., 2005 report that sertraline did not improve cognitive function when compared to placebo in depressed patients. McIntyre et al., 2014 report statistically significant improvement in processing speed with vortioxetine 10 mg while no improvement were observed when vortioxetine 20 mg was compared with placebo. Ferguson et al., 2003 combined various cognitive test used in measuring processing speed (along with including CRT) and reported a combined processing speed score. Paroxetine showed an initial increase in the scores but the scores dropped later by a small degree and were not significantly different from baseline by the end of study.

Systematic Review of Studies involving Digit Symbol Substitution Test (DSST WAIS-III)

The DDST assesses memory, attention and processing speed. The test involves matching symbols with their corresponding numerical digit within a specified time limit. There were three studies that evaluated the effect of second-generation agents by DSST (Table 9.).

Table 9. Studies included under DSST WAIS-III test

RefWorks Id #	Author/ Year	Treatment group	Comparator group
2389	Katona et al., 2012	Vortioxetine, Duloxetine	Placebo
2652	Culang et al., 2009	Citalopram	Placebo
3593	McIntyre et al., 2014	Vortioxetine	Placebo

Although 3 studies were obtained, only 2 were used for carrying out the systematic review. Data provided by Katona et al., 2012 was insufficient to calculate the effect size needed for carrying out a meta-analysis. Katona et al., 2012 reports statistically significant improvement in attention and processing speed with vortioxetine while no difference in case of duloxetine when compared with placebo. Culang et al., 2009 reports that citalopram responders showed more improvement in psychomotor speed than non-responders but this improvement was not greater when compared to placebo responders or non-responders. No information was provided comparing the active drug with placebo for change in cognitive function. McIntyre et al., 2014 shows statistically significant improvements in attention and processing speed with both 10 mg and 20 mg doses of vortioxetine treatment when compared with placebo.

CHAPTER 5

DISCUSSION

This chapter discusses the key findings of systematic review and meta-analysis to evaluate the effects of second-generation antidepressants on cognition. The study findings were compared with previously published reviews. The chapter also includes the limitations and strengths of this systematic review and meta-analysis.

Key Findings and Discussion

This systematic review and meta-analysis evaluated the scientific literature to study the effect of second-generation antidepressants on cognitive function in adults with depression. The findings show that there were 43 unique neurocognitive tests to evaluate cognition. The most frequently used ones are Mini-mental state exam (MMSE), Stroop Color-Word Test (SCWT), and Choice reaction time task and Digit Symbol Substitution Test (DSST). Many selected studies lacked sufficient statistical detail to help calculate the effect size for meta-analysis. Also the use of different reporting methods within same tests led to further complexities which prevented us from conducting a meta-analysis for Stroop Color-Word test, Choice reaction time task, and Digit Symbol Substitution Test WAIS-III. Hence a systematic review was carried out to capture the available evidence for these scales.

The meta-analysis conducted on six studies which had used MMSE to measure cognitive function showed no difference in the effect of second-

generation antidepressants and placebo on global cognition. The findings suggest that there is no effect of second-generation antidepressants on global cognition; however, it is possible that second-generation antidepressants might affect specific cognitive domains which were not captured by MMSE. This is consistent with Biringer et al., 2009 which concluded that SSRIs generally did not affect cognitive function. Consequently, more research is needed to evaluate the effects of second-generation antidepressants on specific domains of cognition, namely, attention, executive function, memory and processing speed.

Systematic review of studies involving Stroop Color-Word test, Choice Reaction time task, and Digit Symbol Substitution Test WAIS-III suggest variable evidence regarding the effects of second-generation antidepressants on specific domains of cognition. Therefore, the individual study findings are reported to provide evidence of variability.

The systematic review conducted on four studies which had used Stroop Color-Word test yielded positive results with two studies; namely Hoffman et al., 2008 and McIntyre et al., 2014 having a combined sample size of almost 13 times that of the non-significant study which suggests possible improvement in executive function with second-generation antidepressants compared to placebo.

The systematic review conducted on four studies which had used CRT yielded mixed results with one study, having a large sample size (n=598) reporting improvements in attention and processing speed in depressed patients treated with low dose second-generation antidepressants. The sample size of

this large study was almost 30 times that of the non-significant study which suggests greater confidence in its findings and further suggests possible improvement in attention and processing speed with second-generation antidepressants compared to placebo.

The systematic review conducted on three studies which had used Digit Symbol Substitution Test suggested mixed evidence. Although conflicting results were seen for second-generation antidepressants within a same study (Katona et al., 2012) which had compared SMs and SNRIs with placebo; study by McIntyre et al., 2014 had the highest sample size (n=591) and it showed significant improvement in memory, attention and processing speed with second-generation antidepressants compared with placebo.

Limitations

In spite of addressing the shortcomings of previous reviews, the present study had several limitations. Firstly, the grey literature was not included; it represents the evidence that does not get published by usual commercial channels (Auger, 1994) or indexed by major research databases. It is a known fact that studies that report positive findings are more likely to get published (Begg and Berlin, 1989; Easterbrook et al., 1991; Dickersin and Min, 1993; Stern and Simes, 1997; Egger and Smith, 1998). This is referred to as publication bias. This might lead to inclusion of more studies that report a positive finding in the meta-analysis resulting in overestimation of the treatment effect leading to a false-positive result (Zlowodzki et al., 2007). However, in order to address this

issue, we conducted tests for publication bias for the MMSE studies which showed absence of publication bias.

The search was limited to English language publications only which may have resulted in exclusion of relevant studies that were written in a non-English language. Although there was an inclusive approach towards study design by selecting both RCTs as well as observational studies, the selected studies were mainly RCTs for our review. The evidence obtained from these RCTs lack external validity as it does not take into consideration the presence of comorbidities along with treatment adherence issues encountered in real world settings.

Another major limitation is the use of diverse neurocognitive tests limiting the ability to combine evidence for a cognitive domain. There is a wide variation in the measurement of cognitive functions with use of multiple tests for measuring single outcome that leads to a lack of common ground to compare and combine evidence from different studies. In addition, this difference is further compounded by use of different versions of the same test. E.g. Digit Symbol Substitution Test (DSST) - WAIS-III and Digit Symbol Substitution Test (DSST) - WAIS-R. Consensus conferences among experts are needed so that a few reliable and valid cognitive tests representing a single cognitive domain are identified which can assist in measuring the cognitive impact of antidepressants. For instance, MMSE is a generic all-purpose non-selective cognitive test which can be used in all the studies. In addition, the use of heterogeneous tests might also suggest a possible hidden bias to selectively report and discuss only those

tests which show positive/significant results. This phenomenon was encountered with regards to selective reporting of the significance of the results (undisclosed results in case of CRT and SCWT) in Culang et al., 2009. This issue can be tackled by registration of clinical trials along with the details of their planned procedure and outcomes of interest.

In case of certain cognitive tests, due to a familiarization effect, ceiling level of test performance is quickly reached leading to masking of the real cognitive impact due to antidepressant therapy. It is important to control for this learning effect during the course of the study, as it can affect the outcome (Amado-Boccara et al., 1995).

Another limitation is the incomplete reporting of test statistics which prevents the performance of meta-analysis. For instance, in some studies, only graphical portrayal of change in cognitive functions was reported without providing numerical values. The underlying reason for this inadequate reporting may lie in that fact that very few studies had cognitive functioning as their primary outcome. In most of the studies, cognitive outcomes were a secondary outcome and hence were not in focus.

This review refers to SSRIs, SNRIs, SMs and Miscellaneous drugs under a single umbrella term. However all of these drug classes differ with respect to their mechanism of action and also their effect's on cognition. All the studies in the MMSE meta-analysis were SSRIs, CRT and SCWT had a mix of SSRIs and SMs, while DSST had a mix of SSRIs, SNRIs and SMs. Such small sample of

studies within each cognitive test makes it difficult to combine the effect of second-generation antidepressants on cognition. There is a lack of studies assessing the effects of desvenlafaxine, venlafaxine, levomilnacipran, fluvoxamine, nefazodone, trazodone, vilazodone, bupropion and mirtazapine on cognitive in depression. Most of the primary studies include in our review, are based on the use of a single medication only. However, this is not the case in a real world scenario where several drugs are co-administered and might affect the action of antidepressants on cognition (Biringer et al., 2009).

Strengths

Due to strict selection criteria, e.g., requiring that the control group participants also had to be depressed resulted in relatively few studies getting included in this review. This was one of the major strengths of our study. The ideal study design to investigate the effect of second-generation antidepressants on cognitive function is the prospective double-blind placebo controlled randomized trial where the participant characteristics of both the placebo control and active treatment group have similar level of depressive symptomatology (Biringer et al., 2009). However, many primary studies compared depressed patients taking active treatment with healthy controls using placebo. Studies having healthy controls were excluded from our study because of the comparability issue. There are two primary reasons for this (Lane and O'Hanlon, 1999): 1) there is an inherent difference between depressed patients and healthy participants. Depressed patients have reduced quality of life, impaired productivity, decreased social functioning and poor physical and mental health

and hence respond positively towards antidepressant therapy. The healthy controls lack depressive symptomatology and experience only the side effects of the treatment. 2) The change in cognitive performance measured by neurocognitive tests should be a valid and proxy measure of change in patient safety and cognitive performance in real life. It is difficult to assume that, the lack of negative cognitive effects in controlled cognitive tests can be directly translated as lack of antidepressant effect on cognition in real life. The reason for numerous healthy control trials in literature may be due to the ethical issue of denying a treatment to a depressed patient on purpose or due to the rationale that cognitive impairing properties of antidepressants are caused by side effects experienced by both healthy participants as well depressed patients (Lane and O'Hanlon, 1999).

This study was one of the first studies to focus on second-generation antidepressants, the most widely used agents for depression. Rigorous methodological techniques were used in performing the systematic review, selecting the studies and assessing their quality. A predefined selection criterion was designed along with prespecified cognitive outcomes of interest which reduced the possibility of selective reporting. Also the primary studies included in our review were conducted in 20 different countries thus including an international body of research which aids in generalizability of the findings across the represented countries. Nearly all of the primary studies included in our review had a good sample size (Average n = 143.3) which increases the reliability of the available evidence. More studies which include reliable and

widely used neurocognitive tests along with reporting necessary statistical detail for computing effect sizes are needed to estimate and quantify the effects of second-generation antidepressants on cognition.

CHAPTER 6

SUMMARY AND CONCLUSIONS

The objective of this study was to determine the effects of second-generation antidepressants on cognition through a systematic review and meta-analysis of recent scientific literature. Electronic searches in Medline, PubMed, PsycINFO, CINAHL, and Embase for English-language abstracts from 1980 through May 2014, supplemented with a manual search from reference lists of relevant review articles was carried out to identify eligible studies. Studies were included if they met the following selection criteria: Population: adults (age≥18) with definite diagnosis of depression based on a validated scale; Intervention: second-generation antidepressants (SGAD) marketed in the United States based on the American Hospital Formulary Service (AHFS) 2014 drug classification; Comparator: placebo or second-generation antidepressants, Outcomes: attention, processing speed, executive function and memory; and Study Design: Randomized Controlled Trials (RCTs) and observational studies. Data management and screening procedures were carried out by using Refworks (ProQuest) and Microsoft Excel workbook.

Data extraction and synthesis was conducted by the primary author using a data extraction form specially designed for this study. Studies were sorted according to type of neurocognitive test used and a minimum of 3 studies per test per study design type was required in order to conduct further systematic review and meta-analysis. The methodological quality of the included studies was assessed by Cochrane risk of bias tool. A random effects model was used to

estimate the pooled effects of antidepressant use on cognitive functioning. Heterogeneity was assessed by I2 testing. Egger's regression test and Trim and Fill method were used to examine for the presence of potential publication bias along with analysis of funnel plots. All analyses were performed using Comprehensive Meta-Analysis, v2.2 (Biostat, Englewood, NJ).

A total of 4,274 abstracts were screened; 342 were retrieved for a full-text review. Of the reviewed full text articles, 17 (13 RCTs and 4 Observational) studies involving a total of 2,437 depressed patients) which met inclusion criteria. Studies were of optimum quality as assessed by the Risk of bias tool. Out of the 43 unique neurocognitive test; Mini-mental State Exam (MMSE), Stroop Color Word test(SCWT), Choice Reaction Time Task(CRT) and Digit Symbol Substitution Test (DSST) were the most common tests used across the studies which fulfilled the selection criteria (minimum of 3 studies per test per study design type) for further systematic review and meta-analysis. Six studies were found eligible for inclusion into the meta-analysis for MMSE and the results were not significant (SMD=0.126; 95%CI -0.046, 0.298; $p > 0.05$). There was no heterogeneity ($I2=0\%$, $p= 0.975$) and publication bias (Egger's regression intercept ($B_0= 0.29359$; 95%CI -1.04627, 1.63344; $p > 0.05$). Insufficient and inconsistent reporting of results for studies involving SCWT, CRT and DSST prevented meta-analysis of selected studies; hence, a systematic review was performed. Four studies were found eligible for SCWT out of which two studies with positive findings which had a combined sample size of almost 13 times that of the non-significant study, which suggests improvement in executive function

with second-generation antidepressants compared to placebo. The systematic review conducted on four studies which had used CRT yielded positive results with one study with sample size 30 times that of the non-significant study showing improvements in attention and processing speed in depressed patients treated with low dose second-generation antidepressants. The systematic review conducted on three studies which had used Digit Symbol Substitution Test suggested mixed evidence with two studies showing significant improvement in memory, attention and processing speed with SMs compared to placebo while one study suggesting otherwise with SNRIs.

In conclusion, meta-analysis of studies using MMSE suggests that SGADs do not affect global cognition but might affect other specific domains. Systematic reviews on studies involving SCWT, CRT and DSST suggest variable evidence regarding the effects of second-generation antidepressants on specific domains of cognition. However, there were indications of possible improvements in executive function, attention and processing speed with SGADs compared with placebo. Further studies involving reliable and widely used neurocognitive tests reporting necessary statistical detail for computing effect sizes are needed to estimate and quantify the effects of second-generation antidepressants on cognition.

APPENDIX A

SEARCH STRATEGIES

Ovid Medline®

1	Bupropion/ or citalopram/ or fluoxetine/ or Fluvoxamine/ or nefazodone/ or Paroxetine/ or Sertraline/ or Trazodone/
2	(citalopram or escitalopram or fluoxetine or fluvoxamine or "lu aa21004" or paroxetine or sertraline or desvenlafaxine or duloxetine or venlafaxine or milnacipran or levomilnacipran or nefazodone or trazodone or vilazodone or vortioxetine or bupropion or mirtazapine).ti,ab,kw,rn.
3	Serotonin Uptake Inhibitors/
4	(serotonin reuptake inhibitor* or sri or sris or selective serotonin reuptake inhibitor or ssri or ssris or Serotonin Norepinephrine Reuptake Inhibitors or snri or snris).ti,ab,kw,rn.
5	antidepressive agents/ or antidepressive agents, second-generation/
6	(antidepressant drugs or antidepressive* or antidepressant treatment).ti,ab,kw,rn.
7	1 or 2 or 3 or 4 or 5 or 6
8	recognition (psychology)/ or "retention (psychology)"/ or "task performance and analysis"/ or auditory perception/ or awareness/ or cognition/ or comprehension/ or concept formation/ or cues/ or executive function/ or higher nervous activity/ or judgment/ or learning/

	or memory, episodic/ or memory, long-term/ or memory, short-term/ or memory/ or mental recall/ or motor skills/ or pattern recognition, physiological/ or pattern recognition, visual/ or perception/ or problem solving/ or psycholinguistics/ or psychomotor performance/ or repetition priming/ or semantic differential/ or speech perception/ or thinking/ or visual perception/
9	(Attention or CIND or Cognition or cognitive decrement or cognitive deficits or cognitive dysfunction or Cognitive Function or cognitive impairment or cognitive improvement or construction or executive function or global function or information processing or intelligence or neurocognit* or neuropsycholog* or verbal memory or processing speed or psychomotor function or psychomotor performance or psychomotor speed or reaction time* or residual depressive symptoms or residual symptoms or verbal function or visual memory or visuoconstruction or visuo-construction or visuospatial function* or visuospatial processing or working memory).ti,ab,kw.
10	8 or 9
11	7 and 10
12	Depression/
13	depressive disorder/ or depression, postpartum/ or depressive disorder, major/ or depressive disorder, treatment-resistant/ or dysthymic disorder/

14	(depression or depressive disorder* or dysthymi*).ti,ab,kw.
15	12 or 13 or 14
16	11 and 15
17	16
18	limit 17 to (english language and yr="1980 - 2014")
19	adult/ or aged/ or "aged, 80 and over"/ or frail elderly/ or middle aged/ or young adult/
20	(adult* or geriatric).ti,ab,kw.
21	19 or 20
22	18 and 21

NLM PubMed

1	Bupropion[mesh:noexp] OR citalopram[mesh:noexp] OR fluoxetine[mesh:noexp] OR Fluvoxamine[mesh:noexp] OR nefazodone[mesh:noexp] OR Paroxetine[mesh:noexp] OR Sertraline[mesh:noexp] OR Trazodone[mesh:noexp]
2	(citalopram[tiab] OR escitalopram[tiab] OR fluoxetine[tiab] OR fluvoxamine[tiab] OR "lu aa21004"[tiab] OR paroxetine[tiab] OR sertraline[tiab] OR desvenlafaxine[tiab] OR duloxetine[tiab] OR venlafaxine[tiab] OR milnacipran[tiab] OR levomilnacipran[tiab] OR nefazodone[tiab] OR trazodone[tiab] OR vilazodone[tiab] OR vortioxetine[tiab] OR bupropion[tiab] OR mirtazapine[tiab])
3	Serotonin Uptake Inhibitors[mesh:noexp]
4	(serotonin reuptake inhibitor*[tiab] OR sri[tiab] OR sris[tiab] OR selective serotonin reuptake inhibitor[tiab] OR ssri[tiab] OR ssris[tiab] OR Serotonin Norepinephrine Reuptake Inhibitors[tiab] OR snri[tiab] OR snris[tiab])
5	antidepressive agents[mesh:noexp] OR antidepressive agents, second-generation[mesh:noexp]
6	(antidepressant drugs[tiab] OR antidepressive*[tiab] OR antidepressant treatment[tiab])

7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
8	recognition (psychology)[mesh:noexp] OR "retention (psychology)"[mesh:noexp] OR "task performance AND analysis"[mesh:noexp] OR auditory perception[mesh:noexp] OR awareness[mesh:noexp] OR cognition[mesh:noexp] OR comprehension[mesh:noexp] OR concept formation[mesh:noexp] OR cues[mesh:noexp] OR executive function[mesh:noexp] OR higher nervous activity[mesh:noexp] OR judgment[mesh:noexp] OR learning[mesh:noexp] OR memory, episodic[mesh:noexp] OR memory, long-term[mesh:noexp] OR memory, short-term[mesh:noexp] OR memory[mesh:noexp] OR mental recall[mesh:noexp] OR motor skills[mesh:noexp] OR pattern recognition, physiological[mesh:noexp] OR pattern recognition, visual[mesh:noexp] OR perception[mesh:noexp] OR problem solving[mesh:noexp] OR psycholinguistics[mesh:noexp] OR psychomotor performance[mesh:noexp] OR repetition priming[mesh:noexp] OR semantic differential[mesh:noexp] OR speech perception[mesh:noexp] OR thinking[mesh:noexp] OR visual perception[mesh:noexp]
9	(Attention[tiab] OR CIND[tiab] OR Cognition[tiab] OR cognitive decrement[tiab] OR cognitive deficits[tiab] OR cognitive dysfunction[tiab] OR

	Cognitive Function[tiab] OR cognitive impairment[tiab] OR cognitive improvement[tiab] OR construction[tiab] OR executive function[tiab] OR global function[tiab] OR information processing[tiab] OR intelligence[tiab] OR neurocognit*[tiab] OR neuropsycholog*[tiab] OR verbal memory[tiab] OR processing speed[tiab] OR psychomotor function[tiab] OR psychomotor performance[tiab] OR psychomotor speed[tiab] OR reaction time*[tiab] OR residual depressive symptoms[tiab] OR residual symptoms[tiab] OR verbal function[tiab] OR visual memory[tiab] OR visuoconstruction[tiab] OR visuo-construction[tiab] OR visuospatial function*[tiab] OR visuospatial processing[tiab] OR working memory[tiab])
10	#8 OR #9
11	#7 AND #10
12	Depression[mesh:noexp]
13	depressive disorder[mesh:noexp] OR depression, postpartum[mesh:noexp] OR depressive disorder, major[mesh:noexp] OR depressive disorder, treatment-resistant[mesh:noexp] OR dysthymic disorder[mesh:noexp]
14	(depression[tiab] OR depressive disorder*[tiab] OR dysthymi*[tiab])
15	#12 OR #13 OR #14
16	#11 AND #15
17	#16 AND english[la] AND 1980:2014[dp]
18	adult[mesh:noexp] OR aged[mesh:noexp] OR

	"aged, 80 AND over"[mesh:noexp] OR frail elderly[mesh:noexp] OR middle aged[mesh:noexp] OR young adult[mesh:noexp]
19	(adult[tiab] OR adulthood[tiab] OR adults[tiab] OR geriatric[tiab])
20	#18 OR #19
21	#16 AND #20

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1	bupropion/ or citalopram/ or fluoxetine/ or fluvoxamine/ or nefazodone/ or paroxetine/ or sertraline/ or trazodone/ or venlafaxine/
2	(citalopram or escitalopram or fluoxetine or fluvoxamine or "lu aa21004" or paroxetine or sertraline or desvenlafaxine or duloxetine or venlafaxine or milnacipran or levomilnacipran or nefazodone or trazodone or vilazodone or vortioxetine or bupropion or mirtazapine).ti,ab,id.
3	serotonin norepinephrine reuptake inhibitors/ or serotonin reuptake inhibitors/
4	(serotonin reuptake inhibitor* or sri or sris or selective serotonin reuptake inhibitor or ssri or ssris or Serotonin Norepinephrine Reuptake Inhibitors or snri or snris).ti,ab,id.
5	1 or 2 or 3 or 4
6	antidepressant drugs/
7	(antidepressant drugs or antidepressive* or antidepressant treatment).ti,ab,id.
8	6 or 7
9	5 or 8
10	pattern recognition (cognitive process)/ or "rumination (cognitive process)"/ or "sense of coherence"/ or associative processes/ or choice behavior/ or chunking/ or cognition/ or cognitive ability/ or cognitive appraisal/ or cognitive discrimination/ or cognitive generalization/ or cognitive impairment/ or cognitive processes/ or cognitive processing speed/ or cognitive

	psychology/ or comprehension/ or concentration/ or concept formation/ or contextual associations/ or critical thinking/ or decision making/ or episodic memory/ or learning/ or long term memory/ or memory decay/ or memory/ or metacognition/ or motor coordination/ or neurocognition/ or neurolinguistics/ or neuropsychology/ or perceptual motor coordination/ or perceptual motor processes/ or physical dexterity/ or problem solving/ or verbal comprehension/ or verbal ability/ or verbal memory/ or visual memory/
11	(Attention or CIND or Cognition or cognitive decrement or cognitive deficits or cognitive dysfunction or Cognitive Function or cognitive impairment or cognitive improvement or construction or executive function or global function or information processing or intelligence or neurocognit* or neuropsycholog* or verbal memory or processing speed or psychomotor function or psychomotor performance or psychomotor speed or reaction time* or residual depressive symptoms or residual symptoms or verbal function or visual memory or visuoconstruction or visuo-construction or visuospatial function* or visuospatial processing or working memory).ti,ab,id.
12	10 or 11
13	9 and 12
14	major depression/ or anaclitic depression/ or dysthymic disorder/ or endogenous depression/

	or postpartum depression/ or reactive depression/ or recurrent depression/ or treatment resistant depression/ or atypical depression/ or "depression (emotion)"/
15	(depression or depressive disorder* or dysthymi*).ti,ab,id.
16	14 or 15
17	13 and 16
18	(17 and ("300".ag. or (adult* or geriatric*).ti,ab,id.)) or (17 not "200".ag.)
19	(adult* or geriatric*).ti,ab,id.
20	18 or 19
21	17 and 20
22	limit 21 to (english language and yr="1980 - 2014")
23	22 and journal.pt.

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S1	TI ((citalopram or escitalopram or fluoxetine or fluvoxamine or "lu aa21004" or paroxetine or sertraline or desvenlafaxine or duloxetine or venlafaxine or milnacipran or levomilnacipran or nefazodone or trazodone or vilazodone or vortioxetine or bupropion or mirtazapine)) OR AB ((citalopram or escitalopram or fluoxetine or fluvoxamine or "lu aa21004" or paroxetine or sertraline or desvenlafaxine or duloxetine or venlafaxine or milnacipran or levomilnacipran or nefazodone or trazodone or vilazodone or vortioxetine or bupropion or mirtazapine)) OR MW ((citalopram or escitalopram or fluoxetine or fluvoxamine or "lu aa21004" or paroxetine or sertraline or desvenlafaxine or duloxetine or venlafaxine or milnacipran or levomilnacipran or nefazodone or trazodone or vilazodone or vortioxetine or bupropion or mirtazapine))
S2	TI (serotonin reuptake inhibitor* or sri or sris or selective serotonin reuptake inhibitor or ssri or ssris or Serotonin Norepinephrine Reuptake Inhibitors or snri or snri) OR AB (serotonin reuptake inhibitor* or sri or sris or selective serotonin reuptake inhibitor or ssri or ssris or Serotonin Norepinephrine Reuptake Inhibitors or snri or snri) OR MW (serotonin reuptake inhibitor* or sri or sris or selective serotonin reuptake inhibitor or ssri or ssris or Serotonin Norepinephrine Reuptake Inhibitors or snri or

	snri)
S3	TI (antidepressant drugs or antidepressive* or antidepressant treatment) OR AB (antidepressant drugs or antidepressive* or antidepressant treatment) OR MW (antidepressant drugs or antidepressive* or antidepressant treatment) \
S4	S1 OR S2 OR S3
S5	TI ((Attention or CIND or Cognition or cognitive decrement or cognitive deficits or cognitive dysfunction or Cognitive Function or cognitive impairment or cognitive improvement or construction or executive function or global function or information processing or intelligence or neurocognit* or neuropsycholog* or verbal memory or processing speed or psychomotor function or psychomotor performance or psychomotor speed or reaction time* or residual depressive symptoms or residual symptoms or verbal function or visual memory or visuoconstruction or visuo-construction or visuospatial function* or visuospatial processing or working memory)) OR AB ((Attention or CIND or Cognition or cognitive decrement or cognitive deficits or cognitive dysfunction or Cognitive Function or cognitive impairment or cognitive improvement or construction or executive function or global function or information processing or intelligence or neurocognit* or neuropsycholog* or verbal memory or processing speed or psychomotor

	function or psychomotor performance or psychomotor speed or reaction time* or residual depressive symptoms or residual symptoms or verbal function or visual memory or visuoconstruction or visuo-construction or visuospatial function* or visuospatial processing or working memory)) OR MW ((Attention or CIND or Cognition or cognitive decrement or cognitive deficits or cognitive dysfunction or Cognitive Function or cognitive impairment or cognitive improvement or construction or executive function or global function or information processing or intelligence or neurocognit* or neuropsycholog* or verbal memory or processing speed or psychomotor function or psychomotor performance or psychomotor speed or reaction time* or residual depressive symptoms or residual symptoms or verbal function or visual memory or visuoconstruction or visuo-construction or visuospatial function* or visuospatial processing or working memory))
S6	S4 AND S5
S7	TI ((depression or depressive disorder* or dysthymi*)) OR AB ((depression or depressive disorder* or dysthymi*)) OR MW ((depression or depressive disorder* or dysthymi*))
S8	S6 AND S7
S9	S8 Limiters - Published Date: 19800101-20141231; English Language
S10	TI ((adult* or geriatric)) OR AB ((adult* or

	geriatric)) OR MW ((adult* or geriatric)) Limiters - Published Date: 19800101-20141231; English Language
S11	S9 AND S10
S12	S9 Limiters - Age Groups: Adult: 19-44 years, Middle Aged: 45-64 years, Aged: 65+ years, Aged, 80 and over
S13	S11 OR S12
S14	s13 Limiters - Exclude MEDLINE records

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1	amfebutamone/
2	citalopram/
3	fluoxetine/
4	fluvoxamine/
5	nefazodone/
6	paroxetine/
7	sertraline/
8	trazodone/
9	escitalopram/
10	desvenlafaxine/
11	duloxetine/
12	venlafaxine/
13	milnacipran/
14	milnacipran/
15	vilazodone/
16	vortioxetine/
17	mirtazapine/
18	(amfebutamone or citalopram or escitalopram or fluoxetine or fluvoxamine or "lu aa21004" or paroxetine or sertraline or desvenlafaxine or duloxetine or venlafaxine or milnacipran or levomilnacipran or nefazodone or trazodone or vilazodone or vortioxetine or bupropion or amfebutamone or mirtazapine).ti,ab,kw,rn.
19	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20	serotonin uptake inhibitor/
21	(serotonin reuptake inhibitor* or sri or sris or selective serotonin reuptake inhibitor or ssri or ssris

	or Serotonin Norepinephrine Reuptake Inhibitors or snri or snris).ti,ab,kw,rn.
22	antidepressant agent/
23	(antidepressant drugs or antidepressive* or antidepressant treatment).ti,ab,kw,rn.
24	19 or 20 or 21 or 22 or 23
25	cognition/ or "confusion (uncertainty)"/ or executive function/ or imagination/ or intuition/ or social cognition/ or "theory of mind"/
26	attention/ or alertness/ or awareness/ or consciousness/ or distractibility/ or mental concentration/ or selective attention/
27	learning/ or comprehension/
28	memory/ or associative memory/ or declarative memory/ or episodic memory/ or explicit memory/ or implicit memory/ or long term memory/ or procedural memory/ or recall/ or recognition/ or semantic memory/ or short term memory/ or spatial memory/ or verbal memory/ or visual memory/ or word list recall/ or word recognition/ or working memory/
29	mental performance/ or mental stress/
30	psychomotor performance/ or job performance/ or task performance/
31	thinking/ or association/ or concept formation/ or critical thinking/ or problem solving/
32	decision making/
33	(Attention or CIND or Cognition or cognitive decrement or cognitive deficits or cognitive dysfunction or Cognitive Function or cognitive impairment or cognitive improvement or construction

	or executive function or global function or information processing or intelligence or neurocognit* or neuropsycholog* or verbal memory or processing speed or psychomotor function or psychomotor performance or psychomotor speed or reaction time* or residual depressive symptoms or residual symptoms or verbal function or visual memory or visuoconstruction or visuo-construction or visuospatial function* or visuospatial processing or working memory).ti,ab,kw.
34	25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
35	24 and 34
36	depression/ or atypical depression/ or dysthymia/ or endogenous depression/ or late life depression/ or major depression/ or treatment resistant depression/
37	(depression or depressive disorder* or dysthymi*).ti,ab,kw.
38	36 or 37
39	35 and 38
40	limit 39 to (english language and yr="1980 - 2014")
41	adult/ or middle aged/ or young adult/
42	aged/ or frail elderly/ or very elderly/
43	(adult* or geriatric).ti,ab,kw.
44	41 or 42 or 43
45	40 and 44
46	medline.cr.
47	45 not 46
48	conference.pt.
49	47 not 48
50	(49 and human/) or (49 not nonhuman/)

51	case report/
52	50 not 51
53	52 not systematic review.ti.

APPENDIX B

DATA EXTRACTION FORM

ID	Variable Name (Coding Instructions)	Values, Text Codes		Page No.
CITATION INFORMATION				
C 1	**Refworks ID #**			
C 2	**PubMed ID #**			
C 3	**Name of coder**			
C 4	**Publication Date**			
C 5	**Citation source(s)**		Main Lit Search	
			Pearling	
			Other (specify):	
C 6	**Secondary cite(s) -** Citation ID #, 1st author, date. Note: Explain relation to other citations, e.g., "This citation contains data from additional follow-up times."			
C 7	**Number of studies reported in this citation**		Note: Default=1	

STUDY LEVEL INFORMATION			
S1	**Study ID** (Default=1, unless ≥2 studies)		
S2	**Primary funding source** (*Check one*)		U.S. Public
			U.S. Private
			U.S. Other: (specify)
			Non-U.S. Other: (specify)
			NA
S3	**Study Design**		Randomized Control trial
			Cross-sectional
			Case control
			Cohort study
			Other (specify):
S4	**Study Location ? State/Province, City, & Country:**		

S5	**Depression Care Setting** (Check one)		Outpatient			
			Inpatient			
			Both outpatient and inpatient			
			Other clinical setting			
			Other *(*Specify*)*			
S6	**Baseline N (total) and Response rate (%)**					
S7	**Age** (Age range, mean & SD, median, age categories, and/or proxy for age-specify.)					
S8	**Gender (# in study-all arms)**		# Male		# Female	
S9	**Marital Status**		% Married		% Single	
S10	**SES** (Education level (years of formal education), employment status, income, SES categories, and/or proxy for SES-specify.)					
S11	**Health Insurance/ Benefits**		% Yes		% No	
S12	**Urbanicity**		Low			
			Moderate			
			High			
S13	**Race/ethnicity**		% African American		% Hispanic/Latino	
			% Asian		% White	
			% Other *(*Specify*)*			
S14	**Baseline risk factors that were reported** *(Check all that apply)*		Old age			
			Dementia/ AD			
			Other risk factors *(specify):*			
			Not described			

COGNITION MEASURES (Outcomes)						
O 1	**Type of Cognitive function** *(Check all that apply)*		Working memory		Episodic memory	
			Attention		Language processing	
			Executive function		Psychomotor performance	
			Processing speed		Other (Specify)	
O 2	**Name of Test used to measure specific cognitive domain**	Working memory				
		Attention				
		Executive function				

		Mental processing speed				
		Episodic memory				
		Language processing				
		Psychomotor Performance				
		Other				
O 3	**Pre-test/Post-test measurement of cognition**		Yes		No	

DEPRESSION AND TREATMENT MEASURES						
D 1	**Instrument used to diagnose depression**		BDI		PHQ	
			Hamilton DRS		CES-D	
			Montgomery-Åsberg DRS		MINI	
			Zung Self Rating		MDI	
			Multiple Instruments		Other (Specify)	
D 2	**Grades of depression assessed**		Mild			
			Moderate			
			Severe/Major			
D 3	**Family history of Depression**		% Yes		% No	
D 4	**Past psychiatric history**		% Yes		% No	
D 5	**No. of past depressive episodes**					
D 6	**Charlson comorbidity Index (CCI)**		No Comorbidity			
			CCI score = 1			
			CCI score > 1			
D 7	**Names of Comorbid disorders present**					
D 8	**Name of antidepressant administered**					
D 9	**Class of antidepressant and**		TCAs			
			SSRIs			

	comparator		SNRIs	
			Serotonin Modulators	
			MAOIs	
			Miscellaneous Agents	
D10	**Control group treatment (RCTs only)**		Usual care	
			Placebo	
			Other (specify)	
D11	**Mean Dose of antidepressant administered**			
D12	**Duration of the treatment**			
D13	**Treatment emergent side effects**			

Operational definitions for the data extraction/coding form variables

C refers to Citation related information

C 1 Refworks ID #

C 2 PubMed ID #

C 3 Name of coder

C 4 Publication Date

C 5 Citation source(s)

C 6 Secondary citation information

C 7 Number of studies reported in this citation

S refers to Study level information

S 1 Study ID

S 2 Primary funding source

Classified on the basis of source of funding sponsorship for conducting the study

S 3 Study design

This includes identifying the type of study design.

Randomized control trial

Cross sectional

Case control

Cohort Study

S 4 Study Location–State/Provinces, City, & Country

This involves the country and the state/city (plural) in which the study was conducted

S 5 Depression Care Setting

This includes the different types of clinical setting in which the depression care/treatment was received (administered)/study was conducted.

Outpatient - health care facility that is primarily devoted to the care of outpatients which is defines as patient who is not hospitalized for 24 hours or more but who visits a hospital, clinic, or associated facility for diagnosis or treatment.

Inpatient - patient who is admitted to the hospital and stays overnight or for an indefinite time, generally several days or weeks

S 6 Baseline N (total) and Response rate (RR %)

Sample size of the participants along with the rate of participation expressed in percentage

S 7 Age

Adults – age ≥18; report as mean, median, range and SD depending on the data provided

S 8 Gender

Number of males/females in all study arms

S 9 Marital Status

Involves married and single (separated, divorced, never married and widowed) categories

S 10 Socio-economic statuses

May not be available in a uniform format. Includes education, employment status, income variables. Studies use different strategies to categorize them. Report the strategy by creating bins as reported in the study.

Education - e.g. of categorizations (<High School, High School, >High School), (Primary School, Junior Middle School, High Middle School), (None, Primary, Secondary) and (Primary or less, Secondary or more)

Employment status - Categorized into employed, unemployed or retired.

Income - reported on a monthly or a yearly scale E.g. (<$25K, $25-45K, $45-75K and >$75K). Preserve the relevant currency without converting it to dollars.

S 11 Health Insurance/ Benefits

Involves insurance against the risk of incurring medical expenses among individuals. Categorized mainly as public(Medicare/Medicaid), private and uninsured.

S 12 Urbanicity

Involves the degree to which a geographical unit is urban usually measured by the number of inhabitants or grading by the level of urbanization as low, medium and high.

S 13 Race

S 14 Baseline risk factors (which could affect cognition) that were reported

O refers to Cognition related information

O 1 Type of cognitive function assessed

O 2 Name of the test used to measure the specific cognitive domain

O 3 Pre-test/post-test measurement of cognition

D refers to Depression related information

D 1 Instrument used to diagnose depression

Refers to the depression scale used to diagnose/measure the prevalence/intensity of depression

D 2 Stage/Grade/Severity of Depression

Classified into mild, moderate or severe/major depending upon the symptom scores or specific cutoffs based on the instrument used. Each scale had a different grading criterion for categorizing mild, moderate or severe depression.

D 3 Family history of Depression

D 4 Past psychiatric history

D 5 Number of past depressive episodes

D 6 Charlson comorbidity Index (CCI)

Predicts the ten-year mortality for a patient who may have a range of comorbid conditions

D 7 Names of comorbid disorders present

D 8 Name of antidepressants administered

D 9 Class of antidepressant

Defined by the AHFS classification 2014

D 10 Control group treatment (RCTs only)

Usual care – no attempt to control for non-specific effects

Placebo – attempt to control for non-specific effects

D 11 Mean dose of antidepressant administered

D 12 Duration of the treatment (in weeks)

D 13 Treatment emergent side effects

APPENDIX C

QUALITY ASSESSMENT OF RANDOMIZED TRIALS

Culang et al., 2009	+	?	+	+	?	+	?
Doraiswamy et al., 2003	+	?	+	+	+	+	?
Ferguson et al., 2003	+	?	+	+	-	-	?
Geretsegger et al., 1994	+	+	+	+	+	+	?
Hoffman et al., 2008	+	?	+	+	+	+	?
Katona et al., 2012	+	+	+	+	+	+	+
Lee et al., 2005	+	+	+	+	?	+	?
McIntyre et al., 2014	+	+	+	+	+	+	+
Munro et al., 2004	+	+	+	+	+	+	?
Munro et al., 2012	+	?	+	+	+	+	?
Robinson et al., 2000	+	+	+	+	+	+	?
Strik et al., 2006	+	-	+	+	+	+	?
Weintraub et al., 2010	+	?	+	+	-	+	?
	1	2	3	4	5	6	7
Judgment	Low	Unclear	Low	Low	Low	Low	Unclear

Key:

‘+ ‘Low risk of bias

‘-‘High risk of bias

‘?’ Unclear risk of bias

1. Random sequence generation (selection bias)
2. Allocation concealment (selection bias)
3. Blinding of participants and researchers (performance bias)
4. Blinding of outcome assessment (detection bias)
5. Incomplete outcome data (attrition bias)
6. Selective reporting (reporting bias)
7. Other bias

APPENDIX D

NEUROCOGNITIVE TESTS USED IN ALL THE STUDIES

Cognitive assessment test	Studies contained Refworks Id #		
	RCT	Obs.	Total #
MMSE	1022, 1093, 2338, 2652, 3022, 3055, 3097, 3910	703, 2933	10
Stroop Colour-Word test	485, 2652, 2775, 3593	2710	5
Choice Reaction Time task (CRT)	2652, 3022* , 3593, 4456§	None	4
Trail Making Test - Part A and B	2775, 3593	703	3
Digit Symbol Substitution Test (DSST) - WAIS-III	2389, 2652, 3593	None	3
Rey Auditory Verbal Learning Test (RAVLT)	2389, 3593	2710	3
Letter-Digit Substitution Test	485	4842	2
Finger Tapping Test	2338	4842	2
Buschke-Fuld Selective Reminding Test	2652, 3097 (different measures)	None	2
Digit Symbol Substitution Test (DSST) - WAIS-R	2775, 3097	None	2
Simple reaction time task (SRT)	3593, 4456§	None	2
Visual Verbal Learning Test	485	None	1
Concept Shifting Task	485	None	1

Wechsler memory scale (WMS-R)	None	703	1
Verbal fluency test	None	703	1
Cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog)	2338	None	1
Digit Span Subtest (Wechsler Memory Scale-III)	2338	None	1
Letter Fluency	2338	None	1
Digit Symbol Modalities Test	2338	None	1
Judgment of Line Orientation	2652	None	1
WAIS III digit span	None	2710	1
Pattern recognition memory (PRM)	None	2710	1
Paired associates learning (PAL)	None	2710	1
Delayed matching to sample (DMS)	None	2710	1
Spatial recognition memory (SRM)	None	2710	1
Reaction time (RTI)	None	2710	1
Ruff 2 & 7 Test total	2775	None	1
Logical Memory Subtest from the WMS	2775	None	1
Verbal Paired Associates Subtest from the Wechsler	2775	None	1

Memory Scale (WMS)			
Animal Naming	2775	None	1
Controlled Oral Word Association Test (COWAT)	2775	None	1
Digit Span Subtest from the WAIS-R	2775	None	1
Critical Flicker Fusion Threshold (CFFT)	3022	None	1
Compensatory Tracking Task (CTT)	3022	None	1
Mental Arithmetic Test (MAT)	3022	None	1
Sternberg Memory Scanning Task (STM)	3022	None	1
Korean-Wechsler Adult Intelligence Scale	3022	None	1
Expressive one-word picture vocabulary test-revised (EOWPVT-R)	3055	None	1
Hopkins verbal learning test-revised (HVLT-R)	3055	None	1
Rivermead behavioral memory test narrative recall subtest	3055	None	1
WISC-R Block design subtest (Wechsler intelligence scale for children- revised)	3055	None	1
Perceived Deficits Questionnaire (PDQ)	3593	None	1

Spike card test	None	4842	1

*= exploded term, no combined estimate available; §= combined with other test to give a factor score, individual score not available

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