A Review of Modern Antidepressants' Effects on Neurocognitive Function

Eva Biringer*[,1], Arvid Rongve[1] and Anders Lund[2]

[1]*Section of Mental Health Research, Division of Psychiatry, Helse Fonna HF, Haugesund, Norway;* [2]*Section of Psychiatry, Institute of Clinical Medicine, University of Bergen, Norway*

Abstract: The present paper reviews the current literature on modern antidepressants' effects on neurocognitive function. Today, it seems justified to state that SSRIs in general do not affect cognitive function. However, there exists some evidence that paroxetine is associated with a somewhat lower performance on neurocognitive tests than other sub-groups of SSRIs. Further, studies have consistently found sertraline to be better with regard to cognitive function compared to other SSRIs. There is a lack of studies assessing effects of RIMAs and $\acute{\alpha}_2$-receptor antagonists on cognitive function. Some evidence suggests that the latter may have negative effects on cognitive function. Other studies suggest that reboxetine, bupropion and SNRIs may be more beneficial with regard to cognitive function than other antidepressants. However, the question whether these medications may actually improve cognitive function to a higher level than expected from improvement in depressive symptomatology, remains unclear. Clinical, social and emotional factors are important for cognitive function and these factors should always be taken into consideration when assessing effects of modern antidepressant therapy on cognitive function.

Keywords: Antidepressant, cognition, SSRI, SNRI, bupropion, reboxetine

1. INTRODUCTION

It is well established that Tricyclic Antidepressants (TCAs) have sedative effects and frequently affect cognitive function [1-3]. However, when the newer Selective Serotonin Reuptake Inhibitors (SSRIs) were introduced to the market in the late 1980s, there was great optimism. One of the reasons for this was the presumption that these newer medications would have no negative effects on cognitive function. It was even postulated that the SSRIs would show beneficial effects on cognitive function [4]. The same is true for other groups of newer antidepressants; Selective Noradrenaline- and Serotonin Reuptake Inhibitors (SNRIs), reboxetine, and bupropion, which all theoretically could improve arousal and attention due to their noradrenergic and dopaminergic effects [5].

At present, many studies on the relationship between use of antidepressant medication and cognitive function have been performed. However, regarding the newer classes of antidepressants, results have been unequivocal regarding if and to what extent these medications affect cognitive function [2, 3, 6, 7].

If we depict a theoretical model involving neurophysiological changes, depressive symptomatology, cognitive function, and medication effects (Fig. **1**), it immediately becomes clear that these associations are complicated and poorly known. Pathways and directions of effects remain unclear. For instance, common neurobiological changes may underlie both depressive symptomatology and cognitive changes during an episode of depression. Effects on cognitive function of antidepressant medication may work through their effects on depressive symptomatology, because improvement in depressive symptoms after use of antidepressant medication may lead to less fatigue and more motivation in the test situation [8]. Alternately, the effect of these medications on cognitive function may primarily be due to their pharmacodynamic effects, i.e. effects on cognitive function that are mediated by neurophysiological changes in the brain [9]. Or, more speculatively, there may be a direct effect of antidepressants on symptomatology (placebo effect).

The relationship between antidepressant use and cognitive function should ideally be explored in prospective double-blinded randomised studies with placebo controls. Groups of patients on one particular type of antidepressant medication should be compared to groups with comparable levels of depressive symptomatology and similar clinical characteristics on placebo medication. Cognitive function should be thoroughly measured with neurocognitive test batteries with high validity that include tests of the main neurocognitive dimensions.

However, literature searches in the databases EmBase, MedLine and PsycInfo reveal that surprisingly few randomised controlled studies with neurocognitive tests as outcome measures are published. This lack of methodologically strict studies may reflect: 1) that depressive disorders are severe conditions and randomising patients into study groups (in which some patients receive placebo medication) is considered unethical, and; 2) that neurocognitive testing is resource- and time consuming. Bearing the latter in mind, it is understandable, but not justifiable, that pharmaceutical companies and other investigators rely on short self-report instruments of perceived cognitive function as outcome measures or neglect to collect information about cognitive function at all when assessing antidepressants' effects.

*Address correspondence to this author at the Section of Mental Health Research, Division of Psychiatry, Helse Fonna HF, Haugesund, Norway;
E-mail: eva.biringer@helse-fonna.no

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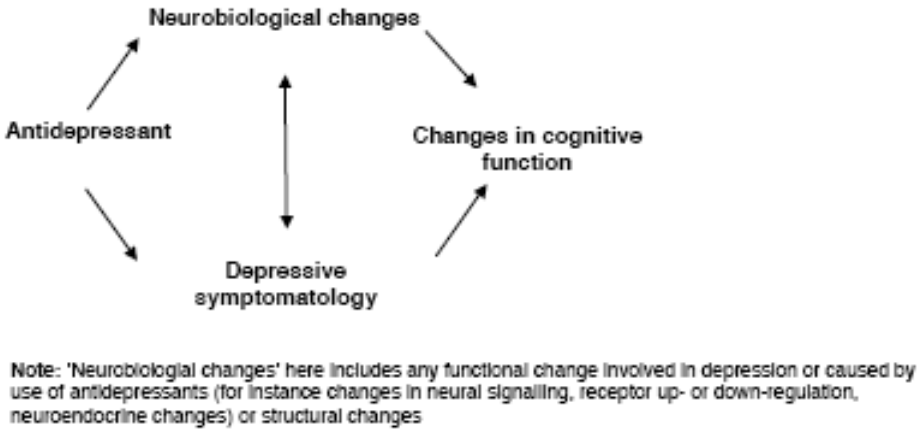

Fig. (1). Theoretical model for confounding and mediating factors on effects in the relationship between antidepressants and cognitive function in depression.

1.1. Neurocognitive Function – Constructs and Measurement

Assessment of neurocognitive function is normally done by using a battery of neurocognitive tests [10-12]. Test batteries often include both pen and paper tests and computerised tests. Neurocognitive test measures are often grouped into the following domains of function: attention, memory function, psychomotor speed, and executive function [10-12]. These constructs are theoretical, although they are supported by empirical evidence. Completing a neurocognitive task involves the use of various domains and sub-domains simultaneously. Further, there is no single test measuring one specific domain only. The heterogeneity of tests makes comparisons of results across studies difficult when different tests have been used as indicators of the same neurocognitive domains. Keeping this in mind is important when reading research reports within this field.

In research using neurocognitive test batteries, significance testing is most often used to detect differences between groups of subjects [11].

1.2. Cognitive Function in Depression

Previous research has made it clear that depressive symptomatology is associated with reduced neurocognitive function [11, 13-19]. Deficits in memory function [20, 21], attention [14, 21-23], executive function [13, 14, 20, 23-26], and psychomotor speed [22, 23, 27, 28] have been reported in depressed patients as compared to healthy controls. The inverse relationship between depression and neurocognitive function has also been detected in studies on patients free of medication [29-31].

1.3. Antidepressants, Neurobiological Changes, and Cognitive Function

1.3.1. Neurobiological Changes in Depression

In depressive disorders, there are several neurobiological abnormalities that may be relevant for cognitive function [32]. Research performed from the 1950s and onwards has revealed that transmission is disturbed in several neurotransmitter systems, in particular in the serotonergic and noradrenergic systems. However, the dopaminergic, cholinergic, and GABA-ergic systems are also known to be involved in the pathophysiology of depression [32, 33]. Intervention in one of these neuroregulatory feedback systems by means of a pharmacological compound inevitably leads to changes within the other systems [33-35].

Functional neuroimaging studies have identified neurophysiological abnormalities in several areas of the brain [36-38]. However, some evidence exists supporting the view that the correlates of changes in regional brain activation are normalised when the depressive symptoms attenuate during antidepressant therapy [39, 40]. Further, computerised tomography (CT) or magnetic resonance imaging (MRI) have detected structural changes in the brain in patients with long-standing depression as compared to healthy controls [41-43]. Four central hypothesised mechanisms for how depression, neuronal functioning, and cognitive changes are related are presented below [9]. These are relevant because antidepressants interact with these mechanisms, thus possibly leading to improved cognitive function [9].

1.3.2. Antidepressants and Normalisation of Serum-Cortisol

A prolonged increase of serum levels of cortisol has been demonstrated in depressed patients, or at least in a sub-group of depressed patients [33, 44]. This increase is most likely due to a stress-reaction that is part of the depressive condition itself, or it may be caused by a dysfunction in the feedback-regulation of the Hypothalamic-Pituitary-Adrenal (HPA-) axis associated with depression [9, 33]. Cortisol may have a neurotoxic effect, and dysfunctional regulation of this corticosteroid has been linked to loss of volume in hippocampus and to memory problems [42, 44-47]. Some evidence exists that prolonged use of antidepressant medication may lead to a reduction of adrenocorticotropine (ACTH) and cortisol in serum [9] and to improved memory function [48]. Such a "normalisation" of the function of the HPA-axis may be one of the reasons why antidepressant medications and improvement in depressive symptomatology are associated with improvement of cognitive function.

1.3.3. Brain-Derived Neurotrophic Factor (BDNF) and Increased Neurogenesis

Brain-Derived Neurotrophic Factor (BDNF) is a neurotrophine produced in the glial cells of the brain [9]. BDNF

is involved in cell growth and –differentiation. Based on animal studies using induced stress paradigms, it has been hypothesised that depression is associated with lower neurogenesis [32, 49]. Newer research indicates that BDNF may mediate the increase in neurogenesis that takes place during use of antidepressant medication [9, 49-51].

1.3.4. NMDA-Receptors and Long-term Memory

Activation of N-Methyl-d-Aspartate- (NMDA-) receptors seems to be involved in the long-term potentiation that is important for memory function [9]. Antidepressants bind to these receptors (as antagonists), thus there is a potential link between antidepressants and improved long-term memory function [9].

1.3.5. The Dopaminergic System and Attention

Finally, antidepressants may influence arousal and attention due to their effects on the dopaminergic transmitter system. Increased dopaminergic activity leads to increased arousal and attentional ability [5, 34, 52]. The anergia and apathy frequently seen in clinical depression may be related to low dopaminergic activity in parts of the brain [53]. Further, findings from studies on healthy participants imply that drugs with dopaminergic effects, such as sertraline or bupropion, may also increase attention in patients [34].

2. EFFECTS OF ANTIDEPRESSANTS ON COGNITIVE FUNCTION

2.1. Antidepressants with Anticholinergic and Sedative Properties

Table **1** shows the degrees of sedative- and anticholinergic effects for various sub-groups of antidepressants. Most of these sedative effects can be accounted for by the drugs' anticholinergic and/or antihistaminergic properties [1, 32]. However, also ά-adrenergic receptor blockade may cause sedation or dizziness. All medications with sedative effects are likely to affect cognitive function. This is particularly true with older groups of antidepressants, in particular the TCAs [1], but also the presynaptic $ά_2$-receptor antagonists are characterised by sedative effects [4].

2.1.1. TCAs

A number of studies have shown that TCAs affect cognitive function, both when depressed patients on TCAs are compared to patients taking placebo medication [54] or SSRIs [54]. Previous studies have shown that dose [3], time since last administration [3] and plasma concentration of the drug [1, 55-57] are factors that determine the extent to which cognitive performance is affected in persons using TCAs. In particular, TCAs affect attention, tempo and memory function [3]. Theoretically, the anticholinergic effects of TCAs may result in poorer long-term memory function because the drugs block acetylcholine-receptors in hippocampus [45]. Doraiswamy *et al.* showed that anticholinergic adverse-effects were associated with less improvement in neurocognitive function over time [58]. Additionally, the blocking of histamine- and α-adrenergic receptors may exert effects on cognitive function after a few weeks of use.

Among the TCAs, amitriptyline is known to have the highest degree of sedative effect [6]. This compound has frequently been used as reference in studies on newer types of antidepressants [2].

The sedative and anticholinergic effects exerted by TCAs are the main reason why such medications should be avoided in patients who are vulnerable with regard to cognitive function. For example, SSRIs and other related compounds are indicated for preferential first use in persons with reduced cognitive function, before TCAs are tried [59]. Alternatively, SNRI's or bupropion should be used.

2.2. Monoamine Oxidase Inhibitors

The older non-selective Monoamine Oxidase Inhibitors (MAOIs) inhibit both Monoamine Oxidase A and B irreversibly. These drugs show limited anticholinergic and sedative properties [60] (Table **1**). These drugs have not shown inverse effects on attention or memory function in depressed patients compared to placebo [61].

2.3. Newer Antidepressants Primarily Affecting Serotonin- and/or Noradrenaline-Reuptake

2.3.1. SSRIs

An overview of double-blind, randomised studies that compare various newer antidepressants and use neurocognitive outcome measures is presented in Table **2**.

2.3.1.1. Comparisons of SSRIs with Placebo

No negative effects of SSRIs on cognitive function were found in clinical studies that compared cognitive function in depressed patients using SSRIs to those receiving placebo [72, 73] or in studies in healthy controls with cross-over designs with placebo condition [74-79].

However, results of studies comparing cognitive function in healthy persons who received short-term administration of paroxetine indicate that paroxetine slightly reduces cognitive function [76, 77]. Furlan *et al.* concluded that performance on cognitive measures was correlated to plasma concentration of paroxetine on tasks of verbal memory [76]. This negative effect of paroxetine on cognitive function may be due to its anticholinergic and sedative properties, which are a bit more pronounced than in other SSRIs. However, Kerr *et al.* reported that paroxetine increased attention slightly (however, with no effect on other dimensions of cognitive function) [80].

2.3.1.2. Effects of SSRIs with TCAs as Reference

A number of studies have compared cognitive side-effects of SSRIs to TCAs [54, 58, 63, 64, 66, 81-83]. SSRIs have proven to be better than the older drugs with regard to cognitive function in all of these studies, with two exceptions. Nickel *et al.* found no differences between groups with regard to attention, memory function and problem solving [64]. Nebes *et al.* reported no differences with regard to cognitive outcome measures, even after adjustment for the effect of level of depressive-symptom load on cognitive function [63].

2.3.1.3. SSRIs Versus Patients Free of Medication

No group-differences in performance on cognitive tests between patients receiving medication and patients free of medication have been reported in studies in which patients

Table 1. Anticholinergic and Sedative Effects by Antidepressant Classification

Antidepressant	Anticholinergic Effect	Sedative Effect
Older antidepressants (Tricyclic antidepressants (TCAs))		
Amitriptyline	+++	+++
Imipramine	++	++
Trimipramine	++	+++
Doxepine	++	+++
Clomipramine	++	+(+)
Desipramine	+	+
Protriptyline	++	(+)
Nortriptyline	+(+)	+
Amoxapine	+	+
Non-selective monoamine oxydase inhibitors (MAOI)		
Phenelzine	+	(+)
Tranylcypromine	+	+
Selective serotonin reuptake inhibitors (SSRIs)		
Citalopram	0	(+)
Escitalopram	0	(0)
Fluoxetine	0	(+)
Fluvoxamine	0/+	+
Paroxetine	+	+
Sertraline	0	(+)
Serotonin agonist-reuptake inhibitors (SARIs)		
Nefazodone	0	+
Trazodone	0	++
Selective noradrenaline- and serotonin reuptake inhibitors (SNRI)		
Duloxetine	0/+	(+)
Venlafaxine	0/+	(+)
Selective noradrenaline reuptake inhibitor (NRI)		
Reboxetine	0	(+)
Reversible monoamine oxidase A inhibitor (RIMA)		
Moclobemide	0/+	(+)
Presynaptic α-receptor antagonists (Tetracyclic antidepressants)		
Mianserine	0/+	+++
Mirtazapine	+	++
Selective noradrenaline and dopamine reuptake inhibitor		
Bupropion (monocyclic aminoketone)	0	0

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have received antidepressant medication according to usual clinical practice [28, 55, 72, 84, 85]. Wadsworth *et al*. showed that SSRI-users and controls performed at similar levels on measures of attention, psychomotor speed, and working memory [72]. However, episodic memory was lower in the SSRI-group than in the control-group. Further, Tsourtos *et al*. demonstrated that depressed, medication-free patients were slower than depressed patients on SSRIs with similar levels of depressive symptomatology [86].

Little is known about the ecological validity of neuro-cognitive test batteries [87]. Consequently, the extent to which the findings from "laboratory" tests of cognitive function are representative of cognitive functioning in eve-ryday situations (e.g. at work) remains largely unexplored.

Table 2. Overview of Prospective Double-Blind, Randomised Studies Using Neurocognitive Outcome Measures

Study	Antidepressant (N=)[a]	Duration (Weeks)	Age (Years)[b]	Dose at Endpoint (mg/d)[b]	Main Findings and Comments
Raskin (2007) [8]	Duloxetin (N=194) Placebo (N=98)	8	73 (5.7) [c] 73 (5.7) [c]	60	Duloxetine > placebo with regard to improvement in cognitive sum scale (based on the Verbal Learning and Recall Test, Symbol Digit Substitution Test, Two-Digit Cancellation Test, and Letter-Number Sequencing Test). Effect mostly attributable to improvement in verbal memory function
Ferguson (2003) [62]	Reboxetine (N=25) Paroxetine (N=23) Placebo (N=26)	8	18-65	20-40 8-10	For reboxetine: Improvement in attention (Cognitive Drug Research (CDR) –factor score Continuity of Attention (Choice Reaction Time: Accuracy, Digit Vigilance: Percentage correct detections and False alarms)) and psychomotor speed (CDR –factor score Combined Speed (Simple Reaction Time, Choice Reaction Time: Speed, Digit Vigilance: Speed of correct detections, Numeric Working Memory: Speed of responses, and Word Recognition: Speed of responses)). Reboxetine > placebo at day 56 (trend only) on attention and speed
Doraiswamy (2003) [58]	Sertraline (N=217) Fluoxetine (N=119) Nortriptyline (N=104)	12	Elderly	83.8 +/-34.7 29.0+/-10.0 70.8 +/-28.9	Sertraline, fluoxetine > nortriptyline on memory (Selective Reminding Test[e] (SLT)) and attention/psychomotor speed (Digit Symbol Substitution Test). Largest correlation between improvement in depression and composite scale of change in cognitive function (SLT Recalled and Retrieved, and Digit Symbol Substitution Test) for sertraline
Nebes (2003) [63]	Paroxetine (N=14)[d] Nortriptyline (N=18) [d] Controls (N=21)	12	70 (6.4)[c] 71 (7.2)[c]		Paroxetine = nortriptyline on working memory (*N* Back Test), attention (Trail Making Test), attention/psychomotor speed (Digit Symbol Substitution Test) and memory (Rey Auditory Verbal Learning Test) in crude analysis and after adjustment for age and level of depressive symptomatology
Nickel (2003) [64]	Paroxetine (N=22) Tianeptine (N=22)	6	25-65	40 75	Paroxetine = tianeptine on attention (Test for Attentional Performance), verbal learning and memory (California Verbal Learning Test, Cogpack), problem solving (Raven Standard Progressive Matrices)
Cassano (2002) [65]	Paroxetine (N=123)[c] Fluoxetine (N=119)	52	76 (7.0)[c] 75 (6.7)[c]	20-40 20-60	Paroxetine = fluoxetine on change in attention (Cancellation Task Test), verbal learning and memory (Buschke Selective Reminding Test, Wechsler Paired Word Test), and overall measures of cognitive function
Bondareff (2000) [66]	Nortriptyline (N=70) Sertraline (N=74)	12	68 (6.6)[c] 68 (6.0)[c]	78 (26) 96 (41)	Sertraline > nortriptyline on MMSE and learning and memory (Shopping-List Task)
Newhouse (2000) [67]	Sertraline Fluoxetine		68 (5.3)[c] 67 (5.9)[c]	50-100 20-40	Sertraline > fluoxetine on attention/psychomotor speed (Digit Symbol Substitution Test) and verbal learning (Shopping List Task)(trend only)
Fairweather (1999) [68]	Fluoxetine (N=15) [d] Dothiepine (N=21) [d]	6	44 (18-70)[c]	20 150	Fluoxetine = dothiepine on memory (Kim's Game), working memory (Serial Subtraction of Numbers). Fluoxetine > dothiepine with regard to improvement of attention (Critical Flicker Fusion Test). Stroke patients in recovery
Finkel (1999) [69]	Sertraline (N=42) Fluoxetine (N=33)	12	74 (3.6)[c] 75 (5.3)[c]	72.6+/-25 28.5+/-10	Sertraline > fluoxetine on attention/psychomotor speed (Digit Symbol Substitution Test). Effect present also after adjustment for depressive symptomatology
Allain (1992) [70]	Moclobemide (N=13) Viloxazine (N=12) Maprotiline (N=12)	6	28 (6.5) 27 (9.3) 27 (9.9)	450 300 150	No differences in improvement in attention (Critical Flicker Fusion Test), memory (word recall, recognition of faces), psychomotor speed (Serial Reaction Times) between groups
Fudge (1990) [71]	Fluoxetine (N=16) Trazodone (N=15)	6	>18	20-60 50-400	Fluoxetine = trazodone on verbal memory (Paired Association), and attention/working memory (Digit Span). Effects present also after adjustment for depressive symptomatology

Note: Subjective interpretations of cognitive constructs and properties of tests have been done when making comparisons across studies. Readers should consult original articles cited for further information about neurocognitive outcome measures. Further, the original articles provide more information about zero-findings.

[a] When available, numbers represent participants at endpoint

[b] Mean +/- standard deviation or range

[c] Information from baseline sample

[d] Treatment responders only

[e] also known as Buschke-Fuld Selective Reminding Test

MMSE= Mini-Mental State Examination

Tianeptine= Selective Serotonin Reuptake Enhancer (SSRE)

Dothiepine=tricyclic antidepressant

Viloxazine=bicyclic antidepressant

Maprotiline=tetracyclic antidepressant

Wadswarth *et al*. compared users of SSRIs and controls by having participants complete diaries about their functioning at work in addition to receiving neurocognitive tests [72]. The study concluded that SSRIs were not associated with perceived human error at work.

2.3.1.3.1 Sertraline

Sertraline is a SSRI that has consistently been shown to be better than other SSRIs with regard to cognitive function. This has been shown when the compound was compared to fluoxetine [58, 67, 69] and citalopram [88]. Several studies have found larger associations between improvement of depression and improvement in test performance for patients on this compound compared to similar associations for other antidepressants [6, 69, 77, 89]. Finkel *et al.* found that the patient group on sertraline showed significantly greater improvement on measures of attention over time than a group taking fluoxetine [69]. However, the sertraline- and fluoxetine- groups performed equally well on a measure of memory function. The difference between groups on measurements of attention was also present after the effect of change in level of depressive symptomatology on cognitive test performance was taken into account. Doraiswamy *et al*. performed a double-blinded study in which elderly patients were randomised into groups receiving sertraline, fluoxetine, or nortriptyline, respectively [58]. The main finding was that the groups on sertraline and fluoxetine improved to an equal extent cognitively upon remission of the depressive symptoms. Further, both sub-groups improved more on tasks of memory function and tempo-demanding tasks than the sub-group on nortriptyline. The highest correlation between improvement of depressive symptomatology and improvement on cognitive test measures was found in the sub-group receiving sertraline. Further, in a recent study in which sertraline was compared to citalopram, differences in favour of sertraline was found on measures of attention (with the exception of Trail Making B), psychomotor speed, verbal fluency and memory after one year of treatment in elderly patients with non-major depression [88].

Sertraline exerts a moderate stimulating effect on the dopaminergic neurotransmitter system [77]. The dopaminergic effect of sertraline is probably the reason why persons on this compound performed better than those on other SSRIs. Other kinds of SSRIs, for instance paroxetine, may have some degree of anticholinergic and/or sedative effects which may, at least theoretically, affect cognitive function (see Table **1**). As expected, sertraline has also been shown to be better with regard to cognitive function than TCAs [55, 58, 66, 90].

2.3.2. Selective Agonist-Reuptake Inhibitors (SARIs)

Fudge *et al*. found no group x time interactions for attention, psychomotor speed, and verbal memory function when they compared groups on trazodone with fluoxetine over six weeks [71]. Analyses were adjusted for level of depressive symptoms. However, Cunningham *et al*. found that cognitive function in patients on trazodone was inferior to those on venlafaxine, using the retardation and cognitive-disturbance factors of Hamilton Depression Rating Scale (HAM-D) as indicators of cognitive function [91]. In a study with cross-over design in healthy participants, findings were conflicting after single- and repeated administrations of nefazodone [92]. Another study found significant improvement of mean scores on a memory task during administration of trazodone compared to placebo condition in depressed patients [93]. In contrast, performance was lower on a task of attention in this study. Lowered attention was also previously shown in healthy study participants after single-dose administrations of this SARI [94-96]. Theoretically, this negative effect on attention may be caused by the sedative effects of trazodone (Table **1**). In conclusion, evidence is still conflicting with regard to the question to what extent these antidepressants affect cognitive function.

2.3.3. SNRIs

In a recent double-blind, randomised trial, Raskin *et al*. found that patients with major depressive disorder (MDD) who received duloxetine for 8 weeks improved significantly more on a sum-scale of cognitive function than did a depressed group on placebo [8]. The effect was mainly driven by improvement in verbal memory. Path analysis showed that there was approximately 80 % direct effect of antidepressant treatment on improvement in cognitive function and about 20% indirect effect of the antidepressant on cognitive function via improvement in HAM-D. Earlier, venlafaxine has been shown to be better than trazodone with regard to cognitive function as measured by the cognitive retardation and disturbance factors of HAM-D in a randomised study in patients with MDD [91]. Another study found improvement in attention, but not in memory function in elderly patients with moderate depression using venlafaxine [97]. Interestingly, duloxetine has been shown to enhance emotional processing in healthy volunteers [98]. Thus, it seems like there is some evidence that SNRIs are beneficial with regard to cognitive function. However, this evidence is still weak and limited.

2.3.4. Reboxetine

Reboxetine is a Selective Noradrenaline Reuptake Inhibitor (NRI) without anticholinergic effects [99]. Newer evidence from animal experiments suggests that reboxetine increases levels of acetylcholine in hippocampus and that this increase may increase memory function [100]. However, neurocognitive studies on depressed patients have failed to show any effects of reboxetine on cognitive function [15, 62]. However, a study performed on healthy volunteers showed lower reaction time and better recall of positive valenced emotional material relatively to stimuli with negative content after administration of reboxetine compared to placebo [101]. This finding may be explained by a combination of emotional changes (antidepressant effect) induced by reboxetine combined with increased arousal caused by higher noradrenergic activity. It shows how antidepressants may modulate the neural processing for emotional material. However, based on the present literature [15, 62], it seems justified to conclude that cognitive function is not affected by reboxetine in depressed patients, despite these interesting findings in healthy volunteer.

2.3.5. Conclusion About Newer Antidepressants Primarily Affecting Serotonin- and Noradrenaline-Reuptake

Based on findings from longitudinal studies with cognitive test performance as outcome measures, it seems reason-

able to conclude that no clinically important relationship between use of SSRIs, SARIs, SNRIs, or NRI and lower cognitive function has been demonstrated. However, evidence exists suggesting that sertraline, reboxetine, or SNRIs should be preferred in depressed patients who experience problems with cognitive function. These recommendations are in line with practice guidelines for the treatment of patients with cognitive impairment [59].

2.4. Other Newer Antidepressants

2.4.1. Reversible Monoamine Oxydase A Inhibitor (RIMA)- Moclobemide

The newer RIMAs are almost free of anticholinergic and sedative effects [102]. The literature is scarce when it comes to studies using neurocognitive outcome measures in the assessment of outcomes after use of these drugs. Studies performed on healthy volunteers have suggested that moclobemide is neutral with regard to cognitive function [103, 104]. To our knowledge, all clinical studies performed on moclobemide with cognitive outcome measures have been negative, i.e., no studies have shown any adverse effects of this RIMA on cognitive function in depressed patients [70, 96]. Roth *et al*. found significant improvements in cognitive function as measured by the Sandoz Clinical Assessment-Geriatric scale (SCAG) -Factor 1 in elderly patients with depression and cognitive decline upon use of moclobemide [105]. Allain *et al*. compared moclobemide to viloxazine and maprotiline in young depressed outpatients and found significant improvement on measures of attention and psychomotor speed in the sub-group on moclobemide, although there was no group x time interaction that reached statistical significance [70]. It appears that moclobemide does not affect cognitive function in any direction. However, there is a lack of studies assessing the effect of RIMAs on cognitive function in depression.

2.4.2. $\acute{\alpha}_2$-Receptor Antagonists

The $\acute{\alpha}_2$-receptor antagonists exert antidepressant effects by blocking inhibitory presynaptic $\acute{\alpha}_2$- receptors. They show affinity for noradrenergic– but also serotonergic– synaptic terminals, and they do possess anticholinergic properties. Some individuals experience a sedative effect which is most likely caused by the drugs' binding to H_1 histaminergic receptors.

The empirical basis is also limited regarding these drugs and cognitive function [1, 6]. In a recent study, a sub-group of depressed patients on mirtazipine performed better than sub-groups of patients on TCAs, SSRIs, or venlafaxine on a global scale used as a valid indicator of driving ability [106]. However, no group differences were found on psychomotor and visual tests. Previously, lowering of immediate memory has been reported in patients taking mianserine [2, 107]. In a meta-analysis by Kerr & Hindmarch, the reported effect-size for adverse effect on speed of processing relative to placebo were comparable with effect-sizes for TCA's for mianserine [6].

2.4.3. Selective Noradrenaline and Dopamine Reuptake Inhibitor (Bupropion)

Since it was launched in 1989, bupropion has proven to be an effective and well-tolerated antidepressant [108, 109]. Bupropion inhibits synaptic re-uptake of norepinephrine and dopamine without any significant direct effects on serotonin neurotransmission [109]. Theoretically, the compound may have a positive effect on attention because of its dopaminergic effect [5]. However, studies with cross-over designs with placebo conditions in healthy volunteers found no effect of bupropion on psychomotor speed, attention and memory [110, 111] or retrieval of material with emotional valence [112].

There seems to be a lack of studies assessing effects of bupropion on cognitive function in depression. One recent study on patients with MDD of unipolar sub-type found that patients on bupropion did as well as healthy controls on a sum-scale consisting of sub-tests of attention, executive function, and psychomotor speed [113].

2.5. Do Modern Antidepressants Improve Cognitive Function Up to a Level Higher Than What Can be Expected from Improvement in Depression?

It has been hypothesised that modern antidepressants actually improve cognitive function [4]. Theoretically, medication with dopaminergic and/or noradrenergic effects may improve cognitive function [77, 100]. However, testing the hypothesis that newer antidepressants improve cognitive function in depressed patients up to a level higher than expected is methodologically difficult because of the clinical and psychosocial confounders that the relationship between medication use and cognitive outcomes are subject to in this group and because premorbid levels of cognitive function are not known. The existing empirical evidence from studies on healthy volunteers [75, 89, 92, 111] and depressed patients [93] regarding a hypothesised beneficial effect on cognitive function upon use of modern antidepressants beyond the effect caused by relief of the depressive symptoms is heterogeneous and weak; we thus lack solid evidence on which to base any conclusions.

3. DISCUSSION

3.1. Limitations of the Current Body of Evidence and Suggestions for Future Studies

Below we discuss several aspects of design and methodology that are relevant for the literature on the effects of antidepressant therapy on cognitive function.

At present, there is a lack of studies assessing the effects of bupropion, reboxetine, SNRIs and RIMAs on cognitive function in depression. Another major limitation of the existing literature is generally a lack of double-blind, randomised placebo-controlled studies [114]. In these studies, patients in the intervention- and placebo- groups should show equally severe levels of depressive symptomatology and they should be comparable in regard to clinical, emotional and social factors. However, when there are ethical reasons for not including placebo-controls, these clinical and emotional factors should be taken into account in other ways (for instance by adjustment for these factors in the statistical analyses). In particular, taking the improvement in cognitive function caused by reduced fatigue and increased motivation upon remission of depression into consideration when assessing

the effects of antidepressants on cognitive function seems important.

Studies comparing samples of patients on various subtypes of antidepressants (or patients free of medication) with regard to cognitive function vary greatly in terms of important participant characteristics such as age, gender, diagnostic sub-types, severity of symptoms, and factors such as medication dose, duration of treatment and methodological tools such as psychometric instruments and neurocognitive tests used. This disparity in study designs, sample characteristics and instruments used, makes comparisons of results across studies difficult. Additionally, patient characteristics that may influence the effect of antidepressants on cognitive function include pharmacokinetic properties, co-morbid somatic disorders, and psychological factors [3]. The clinical and sociodemographic sample characteristics mentioned above may cause confounding-, bias-, and mediator-effects that affect the results from studies on the relationship between use of medication and cognitive function.

Further, most of the present studies are based on the use of one medication only. However, this monotherapy does not reflect clinical reality, in which several drugs are frequently co-administered. Also, treatment periods and follow-up intervals should be longer than the 1-3 months frequently used in clinical trials, in order to investigate to what extent duration of antidepressant therapy predicts cognitive outcome.

Frequently, SSRIs are compared to a tricyclic reference compound without no placebo control. It is well established that TCAs impair cognitive function (as compared to placebo). Consequently, in studies assessing effects of SSRIs relatively to TCAs, comparisons will often favour SSRIs. However, these studies do not provide real answers to the questions of if and to what extent SSRIs affect cognitive function. They merely state that patients on newer antidepressants perform better than patients on TCAs.

Often, depressed patients do not recover completely cognitively after an episode of major depression [19, 115]. However, we advise against interpreting rest-deficits in cognitive performance as signs of prolonged adverse medication effects. Cognitive rest-symptoms may just as plausibly be caused by depressive rest-symptomatology. Alternatively, they may be due to other factors co-existent with depression. Depressed patients may also have had a lower premorbid starting point cognitively (premorbid vulnerability) compared to healthy controls.

Several of the studies included in the present review have used very narrow neurocognitive test batteries in the assessment of cognitive function. In general, smaller test batteries have lower sensitivity to cognitive changes than broader batteries, and some of the studies may have missed aspects of cognitive function.

In the scientific papers included in this review, conclusions are most often based on results from significance testing. Effect sizes for the associations studied are seldomly reported. Evaluation of how important the effects detected are is difficult when their strengths are unknown. Further, making comparisons across studies is easier when commonly used estimates of effects are reported. Results from significance testing depend on sample sizes. Many of the studies reviewed include only few participants (small sub-groups) and group differences may have been lost due to Type II errors. In addition, significance testing does not provide answers to whether or not findings are clinically relevant. That is, group differences that are statistically significant may be of no importance for the patients' well-being and everyday functioning [11].

There may exist a publication bias on the question of antidepressants' effect on cognitive function caused by over-representation of studies with significant findings of adverse effects on cognitive function. Thus, in future studies with zero-findings with regard to effects of antidepressants on cognitive function should be published more often.

There exists evidence from *in vitro* and *in vivo* studies that neurobiological changes in the depressive disorders are affected by antidepressants [11]. In order to throw light on these mechanisms, future studies should more often include indicators of neurobiological changes in addition to neurocognitive tests.

CONCLUSION

There is little evidence that SSRIs adversely affect cognitive function as measured by neurocognitive tests. However, we cannot completely exclude the possibility that some subtypes of these medications lead to a somewhat lower performance on such tests. This may be true for paroxetine. Studies have consistently found sertraline to be better with regard to cognitive function compared to other SSRIs. There exists evidence suggesting that reboxetine, bupropion and SNRIs are more beneficial with regard to cognitive function than other antidepressants. But the question whether these medications may actually improve cognitive function to a higher level than expected from improvement in depressive symptomatology itself, remains unclear. However, these medications should be preferred in patients who are vulnerable with regard to cognitive function.

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