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Cognitive Dysfunction in Major Depression: From Assessment to Novel Therapies

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Abstract

Major depressive disorder (MDD) is a disabling disease associated with profound functional impairment. Cognitive deficits, increasingly recognized as a core feature of MDD, reduce educational, occupational and social outcomes, and impair quality of life and functionality. Unlike cognitive impairments associated with schizophrenia (CIAS), cognitive impairments in depression have been under diagnosed and are poorly understood. Consensus has yet to be reached regarding the nature of these deficits, their appropriate assessment and treatment options. It is unclear whether existing treatments have an impact on cognitive deficits. Here, we conduct a thorough and extensive review of recent published work on this unmet clinical need (2014-2018). We evaluate the validity of available assessment tools, and examine the evidence for efficacy of current and novel pharmacological therapies. From our analysis, we have established that cognitive deficits are indeed widespread in MDD patients. The THINC-it tool, a recently validated and sensitive cognitive assessment instrument, shows promise for earlier detection of Cognitive Impairment Associated with MDD and could be easily applied in clinical practice. Several potential novel therapies are emerging. Methodological inconsistencies and small underpowered studies, however, have led to conflicting results and inconclusive evidence. Our recommendations include: development of a standardized neurocognitive test battery for MDD, improving clinical trial design, investigating sex differences, and patient stratification. These changes should support the development of improved therapeutic strategies for cognitive dysfunction in MDD patients, as well as facilitate their use in clinical practice.

Keywords

Cognition, major depressive disorder, cognitive deficits, neuroinflammation, pharmacotherapy, patient stratification, THINC-it,

List of Abbreviations

ACC	Anterior cingulate cortex
BDI	Beck Depression Inventory
BD	Bipolar depression
CRP	C-reactive protein
CANTAB	Cambridge Neuropsychological Test Automated Battery
CR	Cognitive remediation
CPFQ	Cognitive and Physical Functioning Questionnaire
COX-2	Cyclooxygenase-2
DMN	Default mode network
DSST	Digit Symbol Substitution Test
DA	Dopamine
DLPFC	Dorsolateral prefrontal cortex
DMPFC	Dorsomedial prefrontal cortex
ECT	Electroconvulsive therapy
EPO	Erythropoietin
FED	First-episode depression
fMRI	Functional MRI
HDRS	Hamilton Depression Rating Scale
IL-1 β	Interleukin 1 beta
IL-6	Interleukin 6
LLD	Late-life depression
LF	Life functioning
LDX	Lisdexamfetamine
MRI	Magnetic resonance imaging
MDD	Major depressive disorder
MDE	Major depressive episode
MATRICES	Measurement and Treatment Research to Improve Cognition in Schizophrenia
MADRS	Montgomery-Asberg Depression Rating Scale
NA	Norepinephrine
PDQ-5	Perceived Deficits Questionnaire for Depression-5-item
PFC	Pre-frontal cortex
RCT	Randomised-controlled trial
rMDD	Remitted major depressive disorder
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RAVLT	Rey Auditory Verbal Learning Test
SAMe	S-adenosylmethionine
SSRI	Selective serotonin reuptake inhibitors
SNRI	Serotonin-norepinephrine reuptake inhibitors
TMT	Trail Making Test
TRD	Treatment-resistant depression
TCA	Tricyclic antidepressant
TNF- α	Tumour necrosis factor alpha
UD	Unipolar depression

1. Introduction

Major depressive disorder (MDD) is a highly prevalent and disabling disease. In the United States, 1 in 5 adults experience a major depressive episode (MDE) within their lifetime (Mattingly et al., 2016). Associated with 23-fold increases in social disability and 5-fold increases in disability-related absenteeism, MDD may cause psychosocial impairments equal to, or greater than, chronic illnesses such as diabetes and osteoarthritis (Papakostas et al., 2004). Additionally, depressed patients consistently experience poorer social functioning and higher levels of domestic stress, financial strain, and workplace limitations (Clark et al., 2016).

Cognitive deficits are a core feature of depression. Within the Diagnostic and Statistical Manual of Mental Disorders' (DSM-V) definition of MDD, these relate to "diminished ability to think or concentrate, or indecisiveness" (Regier et al., 2013). Cognitive impairment relates to deficits in attention, executive functioning, working memory, processing speed, learning, episodic memory, and/or visuospatial memory domains. Potentially contributing to anhedonia and psychomotor retardation, cognitive function can be made worse by sleep disruption and fatigue. Conversely, impairment in information processing may be masked by these same symptoms, compounding existing difficulties in recognition and treatment. In a 3-year intervention study, 94% of patients experienced cognitive deficits during an episode of MDD. Of these, 45% had persisting dysfunction during remission (Mattingly et al., 2016). Despite this, only 38% of psychiatrists report using cognitive instruments to screen patients; of these, only 3% were actually deemed appropriate (Belgaied et al., 2014).

Cognitive deficits have considerable impact, and lead to profound psychosocial impairment and disability. Effects include absenteeism, poor workplace productivity and quality of life, increased stress and social impairments, and decreased ability to perform daily functions. Cognitive batteries indicate that processing difficulties exist both during and between MDD episodes with 95% of patients struggling with global cognition. Across all mood disorders, 50-70% of remitted patients have been reported to have cognitive impairments (Seeberg et al., 2018). MDD severity has been significantly associated with reduced cognitive performance, particularly in episodic memory, executive function and processing speed

(Mattingly et al., 2016). Despite this, incomplete treatment and recognition correlate with higher relapse rates and poorer functional outcomes.

Our systematic review aims to conduct a landscape assessment of cognitive deficits in MDD. To do this, we aimed to establish how well cognitive dysfunction has been identified in MDD, the way it is currently measured, and what effects standard and experimental treatments have on cognitive deficits. Our ultimate goal is to provide important recommendations towards an outstanding and thus far greatly neglected need in MDD.

2. Methods

A systematic review was performed using PubMed and ScienceDirect databases, including specifically literature published between 2014 – 2018 to identify the most recent findings in this field. In order to find all material relating to cognitive deficits, studies were identified using a broad collection of terms and then refined according to relevance. Three search groups were used, focusing on depression, cognition and treatments. Terms included: ‘unipolar’, ‘depression’, ‘depressive’, ‘major depression’, ‘major depressive disorder,’ AND/OR ‘cognition’, ‘cognitive’, ‘neurocognition’, ‘neurocognitive’, ‘impairment’, ‘deficit,’ AND/OR ‘antidepressant’, ‘therapy’, ‘treatment’, ‘target’ AND/OR ‘CANTAB’ and ‘THINC’. Additional and relevant studies were also identified from the reference lists of included articles.

The studies included in the current review were all obtained as full text, peer-reviewed, written in English language, focused on MDD, and published within the last twenty years. Articles were excluded if they were duplicates, included sample sizes below 15, existed solely as abstracts, included patients with comorbid conditions (i.e. those with bipolar, schizophrenia, schizoaffective disorder, geriatric depression, or conditions unrelated to unipolar depression), or tested interventions irrelevant to cognition. After applying these criteria, 68 articles were included in the current review (Fig. 1). We have organised our findings into three main areas: 1) measuring the prevalence and impact of cognitive deficits, 2) evaluation of the effectiveness of current antidepressant therapy on cognition, 3) evaluation of novel therapies on cognition.

3. Results

3.1. Measuring the prevalence and impact of cognitive deficits

Given that approximately 40% of currently depressed or remitted patients report impairment in at least one domain, it follows that these deficits encompass a large part of acute disease and recovery (LeMoult & Gotlib, 2018). To understand the true impact of these, we assess their presentation in acute, remitted and first episode depression, as well as their effects on psychosocial functioning and quality of life.

3.1.1 Cognitive deficits in acute and remitted MDD

We first aimed to establish the nature of cognitive impairments in acute and remitted MDD through analysis of the literature. A longitudinal study by Jaeger et al., 2006 examined neurocognitive deficits and disability in life functioning (LF) in MDD (Jaeger et al., 2006). Neurocognitive function was tested twice in 48 MDD patients (32 females and 16 males) hospitalised MDD patients, once at baseline in hospital, and then at 6 months, at which point depressive symptoms showed significant improvement. Despite this change, 60% of patients still scored as significantly, severely, or totally disabled at 6 months follow-up. 87.5% received pharmacological therapy at 6 months, and most individuals taking three medications at baseline later took two. Given the lack of controlled treatment regime and the 'ad libitum' prescribing, no reliable conclusion could be made regarding the direct treatment effect. A tenuous link was observed between 12 patients taking benzodiazepines and LF, where significantly poorer LF at 6 months was noted. The neurocognitive battery used tested seven cognitive domains, detailed in Table 1, with five showing significant association with LF and psychosocial function. Executive function, attention, non-verbal, and learning domain measures were strongly associated with poor functional outcome. Non-verbal, learning and motor function during an episode of MDD were predictive of 6-month LF. With 60% persisting as significantly or severely disabled at follow-up, this identified neurocognitive impairment as a key primary factor hindering functional recovery. Previous findings linking cognition and LF post-remission have been conflicting. A cross-sectional study by Preiss et al., 2009 examined attention, executive function and verbal memory in 97 (51 female, 46 male) unipolar depression (UD) patients during remission (Preiss et al., 2009). Significant cognitive impairments were confirmed in

remitted patients versus controls. Although not found individually, increased depression severity correlated with poorer cognitive ability in the overall sample. All participants had a Montgomery-Åsberg Depression Rating Scale (MADRS) score below 12, indicating they were either symptom-free (0-6) or with some mild depression (7-19). Seventy-nine patients in the sample were on medication, including tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), mirtazapine, or other unspecified antidepressants. Although medicated patients performed better in the Auditory Verbal Learning Test (AVLT) and Trail Making Test (TMT) Part B than non-medicated patients, the small number (N=18) makes conclusions less robust. This makes it difficult to discern whether cognitive impairment was a function of MDD alone or worsened by antidepressant treatment.

Cross-sectional findings by Baune et al., 2010 found the same association (Baune et al., 2010). Immediate memory and attention deficits were significant in 70 patients with previous MDD (44 female, 26 male), compared with healthy controls (N=206). The Mini International Neuropsychiatric Interview (MINI) assessed depression severity. Using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), memory, delayed memory, visuospatial function, language, and attention were significantly worse in the depressed patient group. Visuospatial memory and attention were markedly worse in patients with current active depression. The lasting impact of poor cognition was apparent, highlighting that deficits may persist long after other symptom resolution and into remission. No significant sex difference was noted, although the study was somewhat under-powered for robust statistical evaluation. Mental and social capabilities were detrimentally affected by loss of attention and behavioural execution. This highlights that the relationship between MDD and cognitive deficits requires urgent attention, improved understanding, and treatment.

A systematic review by Hasselbalch et al., 2011 examined 500 remitted patients across 11 studies (Hasselbalch et al., 2011). UD patients reported impaired global cognitive function as previously shown, in addition to reduced attention, memory, and executive functioning compared with 471 healthy controls. Cognitive impairment again persisted beyond single episodes of MDD. In agreement with a lack of efficacy of antidepressant therapy noted by Priess et al., 2009, these studies also reported no significant correlations between antidepressants or cognitive test battery results. Assessment of medication on cognition,

however, was not a primary outcome in any study. In studies by Priess et al., 2009 and Weiland-Fiedler et al., 2004, MADRS scores correlated with sub-syndromal depressive symptoms and poorer cognitive performance, although this finding was not replicated in other studies.

A meta-analysis by Bora et al., 2013 examined the effect of cognitive deficits on brain structure in euthymic MDD patients (Bora et al., 2013). 895 (60.7% female) remitted patients across 27 studies were analysed. MDD patients had significantly lower global cognition scores than healthy controls. Late-onset patients presented with more severe impairments across all domains versus early-onset and control participants, particularly in processing speed, verbal memory, and executive functioning. Using voxel-based morphometry (VBM), reduced grey matter was consistently reported in a focal region of the anterior cingulate cortex (ACC) and in the dorsolateral prefrontal cortex (DLPFC). Multiple-episode patients showed decreased grey matter in the dorsomedial prefrontal cortex (DMPFC), with first-episode depression (FED) patients showing greater reductions in grey matter volume in the amygdala. It would be interesting to investigate further this correlation with cognition.

Rock et al., 2014 confirmed cognitive deficits as an important treatment target in a meta-analysis (Rock et al., 2014). Their review included only one extensive, computerised, language-independent, neurocognitive test battery, the Cambridge Neuropsychological Test Automated Battery (CANTAB), overcoming limitations with non-standardised effect measures, and ensuring consistent testing across several domains, focusing on executive function, memory, attention, and reaction time. 784 symptomatic MDD patients (494 female, 290 male) and 168 remitted patients (54 female, 114 male) were included. Significant deficits were confirmed during acute episodes of MDD that persisted in remission, particularly executive function and attention.

The reviewed evidence makes it clear that cognitive deficits are prevalent in both acute and remitted depression and pose significant detriment to quality of life in patients.

3.1.2 Cognitive deficits in first-episode depression

A meta-analysis by Lee et al., 2012 evaluated neuropsychological deficits during a first episode of depression (FED; Lee et al., 2012). Previously linked to increased relapse rates and recurrent episodes of MDD, the role of cognitive dysfunction in treatment resistance and

remission clearly provides an opportunity for early intervention. This meta-analysis extended findings supporting the potential for early identification of cognitive deficits in FED. 13 studies were reviewed, providing data from 644 FED patients. Cognitive domains tested were consistent with earlier studies, with several measures investigated (Table 1). Cognitive function was found to be significantly worse in first-episode versus recurrent-episode patients, with medium effect sizes measured in six of eight domains, excluding working memory and verbal learning. In terms of treatment effects, antidepressants were associated with increased cognitive flexibility, but also reduced memory and verbal learning. Many samples were limited by poor control for treatment effect, typically treatment by TCAs or typical antipsychotics, and several study results were limited by small sample size as well as poor reporting of clinical characteristics.

More recently, Vicent-Gil et al., 2018 reviewed the role of cognitive predictors in a trial comparing 50 FED patients (30 female, 20 male) with 40 healthy controls (Vicent-Gil et al., 2018). Cognitive measures were assessed at baseline and at 12-month follow-up using an assembled neurocognitive battery (Table 1), which included testing across executive function, language, verbal memory, and processing speed domains. In terms of medication, patients were either antidepressant-naïve or taking equivalent regimes of escitalopram, citalopram or fluoxetine for less than two weeks before the trial started. In contrast to previous findings, FED patients presented with only moderate cognitive impairments when considered as a whole, in comparison to healthy controls at follow-up. Perhaps most interesting is that two clinical subgroups emerged from the FED sample results: 37 'cognitively preserved' patients with no measured cognitive deficits, and 13 'cognitively impaired' patients with dysfunction measured across most cognitive domains. It would seem that cognitive deficits are not homogenous, and that their presentation offers one method by which to stratify patients early in treatment; additionally, it is possible that these 'cognitively preserved' patients may recover more quickly than those with impairments. From this sample, 26% of FED patients, comprising those within the 'cognitively impaired' cluster, displayed significant impairments in working memory, attention, and verbal memory domains. In all FED patients, verbal memory predicted baseline symptoms, whereas executive function and language predicted 12-month symptom severity. Poorer cognitive ability also predicted greater symptom severity and poorer outcomes at

baseline and 12-month follow-up, as also seen in schizophrenia, indicating that early cognitive assessment at disease onset may help support improved outcomes for patients.

The presentation of cognitive deficits is not homogenous in FED patients, despite shared diagnoses and clinical similarities. The influence of cognitive deficits and differences in these at depression onset indicate an apparent need for earlier detection and treatment of these deficits, and for individualised treatment in patient subgroups, e.g. cognitive remediation plus antidepressant therapy in those FED patients with cognitive dysfunction.

3.1.3 Cognitive dysfunction and psychosocial functioning

Given that cognitive deficits persist beyond acute MDEs and into remission, it follows that they can then present significant barriers to functional recovery. Cognitive impairment may thus lead to depression relapse and poor long-term prognosis, and compound existing difficulties with social and global function, as well as employment and workplace productivity.

Knight et al., 2018 sought to define the relationship between impairments in specific cognitive domains and psychosocial functioning in MDD patients (Knight et al., 2018). Results of the Cognitive Function and Mood Study (CoFaM-S) were analysed, in which 182 remitted MDD patients (107 female, 75 male) underwent cognitive testing using three objective batteries: RBANS, Colorado Assessment Tests, and Psychology Experiment Building Language. In order to assess psychosocial ability, the Functioning Assessment Short Test (FAST), a clinician rated interview was used that assesses six functional domains: autonomy, occupational functioning, cognitive functioning, financial issues, leisure time, and interpersonal relationships. In comparison with 110 healthy controls, executive function was concluded to have the most significant effect on psychosocial impairment, workplace functioning, and social cognition in remitted patients.

Knight and Baune, 2018 reviewed the influence of specific executive subdomains on psychosocial functioning (Knight & Baune, 2018). Given that executive function includes several subdomains, including decision making, set-shifting, forward planning, problem solving, working memory, cognitive flexibility, cognitive updating, and inhibition, it follows that executive dysfunction can have significant negative impact upon psychosocial functioning. A sample of 142 patients (88 females, 54 males) were analysed from the CoFaM-

S study, of which 31 had current depression, 52 remitted depression, and 59 were healthy controls. FAST was used to assess psychosocial function, and executive function was measured using a collection of established tests, including the Stroop task, Tower of London, and Berg's Card Sorting Test. Executive subdomains were measured by individual performance in different tasks; forward planning, for example, was gauged using the total moves in the Tower of London task. Within each clinical subgroup, the relationship between executive subdomains and psychosocial functioning was significant. In currently depressed patients, forward planning correlated most significantly with overall psychosocial dysfunction, as well as issues with autonomy, subjective cognition, leisure time, and interpersonal relationships. In remitted patients, however, no one subdomain was identified in sole relation to dysfunction. The cognitive updating subdomain of executive function was found to be negatively associated with reduced psychosocial and occupational functioning.

It is possible that specific testing of forward planning may be a better indicator of functional ability in acute MDD patients. Given that both acute and remitted MDD patients displayed differential executive function relationships, the importance of patient stratification is again highlighted. Lack of separation between the two clinical subgroups may in part be the reason for previous research discrepancies.

Cambridge et al., 2018 performed a systematic review of 28 studies, yielding 6811 adult and elderly MDD patients, in order to identify the strongest predictors of psychosocial functioning outcomes, their longitudinal effects, and any clinical and demographical features that might influence this relationship (Cambridge et al., 2018). Across 23 cross-sectional studies (N=5768) and 5 longitudinal studies (N=1043), performance-based (N=5) or subjective (N=24) assessments measured psychosocial function, with 22 studies concluding a significant relationship between cognitive deficits and psychosocial dysfunction. Within the cross-sectional analyses, 'executive function, attention, memory and global cognition' domains were significantly associated with psychosocial impairments in 'quality of life, social, occupational, and global functioning'. Subjective assessments reported that global cognition and executive function had the greatest influence upon daily functioning impairments, whereas objective assessments highlighted the role of executive function in daily functioning, as well as verbal fluency and attention in social skill dysfunction. Within the longitudinal analyses, two studies

reported that verbal learning, prospective memory and again, executive function were the strongest predictors of functional outcomes at 3- and 6-month follow-up, with the majority of studies concluding that executive function and attention were key domains affecting long-term psychosocial outcomes. Older age and depression severity were also recognised as compounding factors on longitudinal psychosocial outcomes, increasing both the 'susceptibility and magnitude' of these deficits.

Taken together, these findings show that cognitive impairments result in both short- and long-term psychosocial dysfunction. Executive functioning in particular, alongside attention and memory, are most significantly related to poorer functional outcomes. Looking towards the future, further insight into forward planning dysfunction and the positive role of cognitive updating in remission may be key to developing future treatments, as well as targeting the domains highlighted as most significantly related to functional outcomes.

3.1.4 Improved detection and measurement of cognitive deficits

Evidence has established that cognitive deficits are prevalent in acute and remitted depression patients. FED patients also present with cognitive impairment, although, despite shared diagnoses and clinical similarities, these impairments occur at varying degrees of severity. The urgent need for earlier detection and treatment of these deficits is apparent, together with assessment of patients on an individual, rather than collective, level.

Table 1 illustrates the disordered state of current cognitive assessments, where many studies have been limited by extensive, long, and potentially exhausting neurocognitive assessments. With no consensus on which domain is measured by each test, many studies have used different tasks and different formats to measure the same domain. For example, the TMT Part B test is considered by some as a measure of executive function, and by others attentional switching. Where some studies have used single batteries, such as CANTAB or RBANS, others have formulated their smaller batteries using combinations of tests, leading to inconsistent analyses and comparison difficulties. A standardised test battery is critical in order to improve future studies, as attempted by the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) battery in schizophrenia (Marder & Fenton, 2004).

Most recently, Baune et al., 2018 highlighted the THINC-it tool as one method to secure more valid assessment of cognitive function in patients (Baune et al., 2018). In comparison the Mini Mental State Examination (MMSE) or RBANS, the THINC-it assessment is a more affordable, accessible and practical screening tool intended for use during routine clinical assessment. It is available in the format of a rapid, accessible, and language-independent application optimised for several operating systems. Risk factors for relapse and recurrence of depression include residual depression symptoms after treatment, longer duration, and greater severity of disease (Buckman et al., 2018). Earlier detection of cognitive deficits would be a good use of resources and provide long-term benefit to patients. Although frequent re-testing may be valuable for detection, this may be limited by practice effects.

Using objective and subjective measures such as the Perceived Deficits Questionnaire for Depression-5-item (PDQ-5), THINC-it may relieve the long-term impact of poor cognitive function by better detection of these deficits, as well as by facilitating earlier identification and treatment. This is in keeping with findings that cognitive deficits are possible early identification targets, and that cognitive measures may be predictive of future psychosocial impairments, particularly as a means of patient stratification (Lee et al., 2012; Cha et al., 2017). Although it does not predict treatment response, THINC-it could be used by healthcare professionals and patients to measure treatment efficacy and on-going cognitive function, either at home or in clinics. Additionally, the tool may be ideally suited for uncovering signs of potential cognitive dysfunction in high-risk patients before symptoms appear, although conclusive evidence has yet to be found regarding whether cognitive deficits occur before a diagnosis of depression as for psychosis (Keefe, 2014).

McIntyre et al., 2017 validated the THINC-it tool in 90 moderate to severely depressed MDD patients (51 female, 39 male) (McIntyre et al., 2017a). A significant difference was reported between MDD patients and controls, confirming the existence of cognitive deficits in patients. Although the 'gold standard' for neurocognitive testing would be an extensive battery like CANTAB, the THINC-it application is free, simple to use, downloadable to computers, mobile phones or tablets, and can be self-administered. The THINC-it tool is shorter than traditional batteries, with MDD patients averaging at around 10-15 minutes for completion. Assessing the same cohort, Cha et al., 2017 reported THINC-it as a successful

screening measure for cognitive impairment and psychosocial functioning. In the MDD group, loss of more economic days and reduced workplace productivity were significantly associated with greater depression severity, cognitive deficits, and psychosocial impairment. THINC-it detected subjective, patient-reported cognitive function, supplementing objective measures and helping to identify psychosocial dysfunction independent of depression severity scores.

THINC-it is not extensive enough to replace the larger test batteries used in clinical trials, and a more uniform neurocognitive battery remains an unmet research need. Similar to 'Cognigram', an electronic version of the Cogstate Brief Battery (CBB) which is shorter than MATRICS and used in schizophrenia, the accessible, computerised, and language-independent nature of THINC-it does still, however, present several advantages for screening and detection purposes (Cogstate, 2014).

As demonstrated by several studies thus far, a diagnosis of depression is insufficient evidence to confirm either the presence or absence of cognitive impairment. In 262 un-medicated MDD patients (161 female, 101 male), Keilp et al., 2018 confirmed that cognitive performance was not significantly associated with the scores on standard depression severity measures often employed in clinical trials, using the 24-item Hamilton Depression Rating Scale (HDRS) and Beck Depression Inventory (BDI) (Keilp et al., 2018). Cognitive assessment was carried out using a 10-test battery, including Choice Reaction Time (CRT), Wechsler Adult Intelligence Scale (WAIS-III), Continuous Performance Test (CPT), Stroop test, Selective Reminding Test (SRT), Wisconsin Card Sorting Test (WCST), and Go-No-Go tests. Neither subjective cognitive complaints, as measured by the Cognitive Failures Questionnaire (CFQ-25), nor results from depression measures were significantly linked to cognitive performance. Patients meeting certain clinical criteria, however, such as for melancholia or history of substance abuse, showed stronger correlation between depression severity and cognitive impairment than others. In addition, late-onset patients also presented with slower reaction time and reasoning speed, confirming once again the heterogenous nature of cognitive deficits.

Although the CFQ-25 should capture subjective cognitive complaints missed by severity scores and objective battery testing, Keilp et al., 2018 noted that these scores were more indicative of mood, rather than neurocognitive ability. This may challenge the inclusion of subjective measures to broaden cognitive assessment in trials, or at the very least indicate that

such measures and their subsequent results should be interpreted with caution. Cognitive impairment is thus inadequately captured by classic depression rating scales. As the majority of studies use these scores for inclusion and screening, this is a cause for concern. Furthermore, it underscores the need for more accurate, sensitive cognitive screening tools and test batteries.

Ballard et al., 2018 assessed common depression rating scales used in clinical ketamine trials with 76 MDD and 43 bipolar patients (Ballard et al., 2018). Ratings from the BDI, Snaith-Hamilton Pleasure Rating Scale (SHAPS), HAM-D, and MADRS were used to identify the range of symptoms reported. In order to accurately capture the heterogeneity of depression, eight symptom domains were proposed instead of total measure scores from individual ratings, including: depressed mood, tension, negative cognition, impaired sleep, suicidal thoughts, reduced appetite, anhedonia, and amotivation. These unidimensional ratings may be more representative of the range of symptoms experienced by depression patients, thus helping to pinpoint their underlying pathophysiology and consequent treatment options.

In essence, earlier detection and prevention of cognitive deficits in an “at risk” population is necessary to improve functional outcomes. Newly validated tools such as THINC-it may make detection of these deficits easier. Across the majority of clinical trials, however, the measurement of cognitive impairment remains inadequate. This disorganised state of neurocognitive assessment would be best alleviated by the development of one standardised test battery, which should be sensitive and accurate enough to detect varying and highly individual degrees of cognitive impairment in depressed patients.

3.2. Evaluation of antidepressant therapy on cognition

Cognitive impairment has been established as a significant and thus far untreated clinical need in MDD patients, and it is important to consider effects of existing antidepressant therapies on cognitive function.

In this review, the effects of ‘traditional antidepressants’ such as SSRIs sertraline, fluoxetine, escitalopram, paroxetine, citalopram; SNRIs duloxetine, venlafaxine, desvenlafaxine; TCAs nortriptyline and dothiepin, and the norepinephrine-dopamine reuptake inhibitor (NDRI) bupropion will be discussed in relation to their effects on cognition, together with the novel multimodal serotonin modulator vortioxetine and NMDA receptor antagonist ketamine. As

recent literature has discussed antidepressant effects on cognition, this review intends to collate these findings and discuss additional contributions (Keefe et al., 2014; Rosenblat et al., 2015).

3.3.1 Placebo controlled trials of traditional antidepressants in cognitive impairment

In placebo-controlled trials conducted to date (Table 2), the SSRI citalopram and SNRIs duloxetine, desvenlafaxine, and venlafaxine show mixed results. Testing verbal learning, memory, attention, and executive function in an 8-week double-blind trial in 207 elderly MDD patients, Raskin et al., 2007 described significant improvements with duloxetine 60mg on verbal learning and recall (Raskin et al., 2007). Venlafaxine 75-150mg also showed positive results, with Tian et al., 2016 reporting selective improvements in executive control of attention and MDD symptoms after 6 weeks in the Attention Network Test, although in only 34 patients (Tian et al., 2016). With desvenlafaxine 50 mg, Reddy et al., 2016 used the cognitive drug research (CDR) system to show significant working memory improvements over 12 weeks (Reddy et al., 2016). This positive effect may be a direct result of serotonin and noradrenaline reuptake inhibition, improving symptomatology and cognition, although the small sample size of 81 is limiting. Interestingly, Tian et al., 2016 reported that executive control and depression symptom improvement were not correlated, indicating that these effects may potentially occur via different mechanisms.

Regarding the SSRI citalopram, mixed results were found by Culang et al., 2009. After 8 weeks, 20-40mg citalopram non-responders reported impaired verbal learning and psychomotor speed, suggesting that treatment may worsen cognition in patients non-responsive to medication (Culang et al., 2009). Although citalopram responders improved in visuospatial functioning, this effect was no greater than those receiving placebo; improvements in psychomotor speed were also no more significant than those seen in placebo responders or non-responders. These findings suggest that response status may be an indicator of potential negative treatment effects on cognition, and that citalopram presented small but non-significant improvements when compared to placebo.

Taken in combination, these data suggest that SNRIs could potentially improve memory and verbal learning, though small sample sizes and elderly populations limit current

analysis. Although selective improvements have been reported with SNRIs, Table 2 highlights a lack of consistency in the cognitive measures used, compounding problems with generalisability. Further research with larger sample sizes is warranted before firm conclusions can be made, ideally using a standardised test battery. As it is yet unclear whether the positive effects of SNRIs on cognition occurs via improvement of depression symptoms, or by a secondary independent mechanism, more research is clearly required.

3.3.2 Active comparator trials of traditional antidepressants in cognitive impairment

Within active comparator trials (Table 3), the SSRIs sertraline, fluoxetine, escitalopram, SNRIs venlafaxine and duloxetine; TCAs nortriptyline and dothiepin, and NDRI bupropion were compared for effects on cognition.

Doraiswamy et al., 2003 and Culang-Reinleib et al., 2012 both reported cognitive improvement with sertraline 50-200mg. Compared with nortriptyline 25mg and fluoxetine 20mg, Doraiswamy et al., 2003 found that sertraline led to the greatest improvements in depression, verbal learning (SLT) and visual tracking and motor performance (DDST) (Doraiswamy et al., 2003). In 440 patients, baseline cognitive impairments correlated with greater baseline depression severity and older age, and those with greater cognitive deficits also saw greater magnitudes of improvement. Directly comparing with nortriptyline 1mg/kg, Culang-Reinleib et al., 2012 reported that sertraline patients showed significant improvement in verbal learning, and more so than nortriptyline patients, who showed no improvements (Culang-Reinleib et al., 2012). Sertraline also improved memory in non-responders, indicating that effects on cognition may be independent of those on depression symptomatology, consistent with previous suggestions by Tian et al., 2016. Given the small sample size (N=33) and lack of placebo control, further replication studies are warranted. Neurocognitive testing could also have been more rigorous, as domain-specific results and analyses were limited.

Trials by Herrera-Guzman et al., 2009 and 2010, treated 73 patients with either escitalopram 10mg/day (SSRI) or duloxetine 60mg/day (SNRI) for 24 weeks, after which they were assessed for a further 24 weeks following remission (Herrera-Guzman et al., 2009; Herrera-Guzman et al., 2010). Both treatments improved episodic memory, with smaller

improvements also in working memory, processing speed, and motor performance. Upon further analysis, duloxetine had greater beneficial effect on episodic memory than escitalopram, with the latter group recording lower verbal and visual memory scores at the 24-week follow up assessment. At this time-point, it was also confirmed that cognitive deficits persisted beyond the remission phase, and that the SNRI was still superior in improving episodic and working memory. Different results to previous studies may be due in part to more robust study design, i.e. long duration of treatment with a long follow-up period, and more representative sample population, with a mean age of 33 years and extensive application of the CANTAB battery, consisting of individual tests listed in Table 3.

Trick et al., 2004 also investigated the effects of SNRIs, trialling venlafaxine 75mg against the TCA dothiepin 75mg in 88 elderly patients (Trick et al., 2004). Although both treatments achieved therapeutic effects and clinical efficacy, venlafaxine showed a modest improvement in cognition as measured by the Critical Flicker Fusion (CFF) test, indicating CNS arousal. Conversely, dothiepin was associated with decreased CFF performance, linked potentially to its anticholinergic and antihistaminergic pharmacology.

The NDRI bupropion (150-300 and 150-450mg respectively) was tested in two trials by Soczynska et al., 2014 and Gorlyn et al., 2015, comparing efficacy against the SSRIs escitalopram 10-20mg and paroxetine 25-50mg. In 41 MDD patients, Soczynska et al., 2014 found that both bupropion XL and escitalopram significantly improved verbal and non-verbal learning and memory, global function, and work productivity (Soczynska et al., 2014). Gorlyn et al., 2015 concluded that bupropion and paroxetine improved neurocognitive performance across psychomotor, attention, memory and working memory domains in 67 MDD patients with past or current suicidal ideations (Gorlyn et al., 2015). Paroxetine had a slightly greater improvement in psychomotor speed. Although no significant superiority was reported between the two studies, this may be due to the reduced statistical power of small sample sizes. Depression symptom improvement was not associated with improved cognition, once again suggesting that these two effects may occur via independent mechanisms. Gorlyn et al., 2015 also noted that verbal memory improvements correlated with reduced suicidal ideation.

Shilyansky et al., 2016 trialled 1008 MDD patients with escitalopram (SSRI), sertraline (SSRI) or venlafaxine-XR (SNRI), with average doses of 12.3mg, 61.1mg and 83.4mg per day

respectively (Shilyansky et al., 2016). The IntegNeuro battery (listed in Table 3) was used to test 9 cognitive domains: attention, response inhibition, verbal memory, executive function, cognitive flexibility, working memory, decision speed, information processing, and motor coordination. Both individual and group level cognition was assessed to account for possible change in cognitive ability across different subgroups. Participants had not been receiving medication before the trial, and the average age was 37.8 years.

No significant improvements were measured in the majority of domains at trial completion, although some improvement was noted in executive function and cognitive flexibility. Across the other five domains, those with clinical remission saw an equal lack of improvement as patients with active MDD. Results reported that only 4.5% of patients had impairment resolution after treatment, with generally no more than two domains showing a significant effect in any one person. The group that saw this improvement were those with later disease onset. No one antidepressant was recorded as superior in any single patient group, and no significant results were reported regarding sex differences.

3.3.3 Conclusion and limitations of traditional antidepressant trials

In placebo-controlled trials, the SNRIs duloxetine, desvenlafaxine and venlafaxine appeared to be superior to citalopram in terms of cognitive benefit. Yet in terms of active-comparator trials, the results are more complex. Where sertraline has been associated with greater improvements compared to fluoxetine or nortriptyline, duloxetine and venlafaxine have also been reported as superior to escitalopram and dothiepin respectively, and detrimental cognitive effects were reported with dothiepin. Neither escitalopram, sertraline, nor venlafaxine provided significant improvements in cognition. In summary, traditional antidepressants have varying intra- and inter- class-dependent effects on cognition, and no particular antidepressant (or class) has been found to have consistently superior effects on cognition.

It is of interest to note some pharmacological findings. Post treatment with venlafaxine, Tian et al., 2016 reported that improved executive control and depression severity were not correlated, indicating that these are likely underpinned by different mechanisms. A selective effect to improve the executive control of attention, often manifesting in patients as impulsivity, was suggested to be due to increasing DA concentration in frontal, limbic, and

parietal areas. This extends suggestions by Herrera-Guzman et al., 2009 and 2010, where superior action of SNRIs on recovering episodic and working memory was linked to 5-HT and NE stimulating DA release in the DPFLC, driving neural circuits in conjunction with the thalamus and basal ganglia (Herrera-Guzman et al., 2009; Herrera-Guzman et al., 2010). In terms of TCAs, Trick et al., 2004 indicated that cognitive impairment may be associated with the sedative effects of dothiepin, leading to more pronounced difficulties with cognitive and psychomotor functions, particularly in the elderly. Culang-Rienleib 2012 suggested that lack of verbal learning improvements in nortriptyline responders may be due to anticholinergic effects impairing memory. Further research into the advantageous and disadvantageous effects of SNRIs and TCAs would be valuable; such findings could provide evidence for treatment adjustments in existing populations, particularly in the elderly, in order to preserve cognitive function. In addition, further clarity is required as to whether antidepressants can improve cognition independent of their effect on symptom severity.

In terms of limitations, generalisability was questionable due to small samples consisting mostly of elderly patients. Participants ranged from mild to severely depressed, making it difficult to distinguish whether cognitive impairment changed due to treatment, or whether it remained impaired due to disease severity. Cognitive testing varied considerably, as outlined in Tables 2 and 3, and the variety of assessments and their interpretation makes true comparison difficult. The Controlled Oral Word Association Test (COWAT), for example, was cited as a test of verbal fluency, processing speed, or executive function, making the likelihood of methodological inconsistencies high. These results provide further research setbacks, and confirm the need for standardised cognitive test batteries for MDD.

Despite regulatory and research advances recognising cognition as an important target, treatment advances are still unsatisfactory due to the 'patchwork set of methods' used in studies, where methodological difficulties and lack of longitudinal studies are confounding results across the field (Keefe, 2016). This, together with unrepresentative patient ages, variable study designs, lack of gender in the analysis and lack of follow-up data, are limitations that must be overcome.

3.3.1 Novel antidepressants in cognitive impairment

Vortioxetine is a novel antidepressant with unique pharmacology, working as a multimodal serotonin inhibitor at serotonin transporters (SERTs) to inhibit 5-HT reuptake, displaying 5-HT₃, 5-HT_{1D} and 5-HT₇ receptor antagonism, 5-HT_{1A} receptor agonism and partial 5-HT_{1B} receptor agonism (Sanchez et al., 2015). Vortioxetine's 5-HT_{1A} receptor agonist effect has been suggested to inhibit GABA release, promoting secondary release of DA, NA, histamine (HA) and acetylcholine (ACh) in the hippocampus and PFC (Salagre et al., 2018). Ketamine, a non-competitive NMDA receptor antagonist, has been found to be effective in reducing suicidality and depressive symptoms in TRD, and a form of ketamine, esketamine has very recently been licensed by the Food and Drug Administration (FDA) for depression. The evidence for these two treatments will be reviewed in this section (Table 4).

With good tolerability and broad antidepressant effect, the potential of vortioxetine to improve cognitive function is an exciting prospect. In an 8-week randomised control, active reference study, Katona et al., 2012 trialled vortioxetine 5mg (Lu AA21004) and duloxetine 60mg in 453 elderly patients (Katona et al., 2012). Although both treatments were efficacious in improving depression symptoms and Rey Auditory Verbal Learning Test (RAVLT) scores, vortioxetine significantly improved Digit Symbol Substitution Test (DSST) performance, suggesting efficacy beyond the verbal learning and memory improvements reported previously with duloxetine by Katona et al., 2012 and Raskin et al., 2007. Vortioxetine led to significant improvements in processing speed, verbal learning, and recall domains, and given that performance on the DSST requires executive function, this may also have been improved. Over two-thirds of vortioxetine's effect on cognition was due to direct treatment effect, and not by indirect improvement of symptom severity as with duloxetine.

Mahableshwarkar et al., 2015 trialled vortioxetine 10-20mg alongside duloxetine 60mg in an 8-week randomised, placebo-controlled, and active-reference study of 602 MDD patients with self-reported cognitive dysfunction (Mahableshwarkar et al., 2015). The neurocognitive battery employed several objective cognitive measures, as listed in Table 5, together with the PDQ and Cognitive and Physical Functioning Questionnaire (CPFQ) as subjective, patient-reported measures. Where both duloxetine and vortioxetine significantly improved attention/concentration and planning/organization PDQ scores, only vortioxetine significantly improved DSST and TMT-B performance, indicating restored executive function and

quicker cognitive processing speed. Duloxetine did not separate from placebo on DSST performance, and its positive effects on PDQ scores were attributed to improved depression symptoms only, rather than specific pro-cognitive action. Although inclusion criteria only required patient-reported measures of cognition, it was suggested that this reporting system may be more applicable to clinical practice; it will be important, therefore, for future trials to investigate objectively measured deficits at inclusion for comparison.

In an 8-week, randomized, placebo-controlled study by McIntyre et al., 2014, vortioxetine 10-20mg was trialed in 602 MDD patients (McIntyre et al., 2014). Although RAVLT and DSST tests were again used, six other tests, as listed in Table 4, provided a more detailed composite score. Significant improvement was reported in objective measures of executive function, attention, processing speed, learning and memory, with the subjective, patient-reported PDQ also indicating improvement in memory, concentration, and planning/organization. It is worth noting that vortioxetine's improvement of cognition was due to both direct and indirect therapeutic effects. When given at 20mg, vortioxetine showed a more significant improvement in MADRS severity scores disparate from the improvement in cognition, suggesting that these effects do in fact occur by separate mechanisms.

Harrison et al., 2016 investigated which specific domains vortioxetine improves (Harrison et al., 2016). In an 8-week, randomised, placebo-controlled trial, vortioxetine 10mg-20mg was administered to 602 MDD patients, with the DSST used as a primary assessment to analyse effect sizes on executive function, processing speed/attention, and memory. In keeping with findings by Katona et al., 2012 and Mahableshwarkar et al., 2015, vortioxetine again led to improved DSST performance. Harrison et al., 2016 did emphasise that this change does not necessarily mean improvement on any one specific domain; rather, it requires integration of several, more broad cognitive skills engaged by the DSST, which were reflected by changes in the other individual neurocognitive tasks included, noted in Table 4.

Smith et al., 2018 conducted a placebo-controlled, randomised fMRI neuroimaging trial in 96 remitted MDD patients and healthy controls, who were administered vortioxetine 20mg or placebo over 2 weeks to assess neural and cognitive function (Smith et al., 2018). In previous remitted and active MDD patient studies, blood-oxygen-level-dependent (BOLD) signal activation has been shown to increase and maintain hyperactive response during task

performances. When fMRI was applied during the N-back working memory task, vortioxetine showed reduced BOLD signal activation in the dlPFC, left hippocampus, and temporal-parietal areas across both treatment groups, and also led to improved TMT-A performance and PDQ scores. Vortioxetine may thus reduce effort and encourage more efficient recruitment of the default mode network (DMN) and task-positive networks during working memory tasks. This could explain the direct and independent effect of vortioxetine on cognition, specifically on executive function and working memory. These results however, remain limited by the short trial length and lack of objective deficits reported by the remitted sample at the start of the trial.

In a randomised, double-blind, active-comparator study, Vieta et al., 2018 explored the effects of vortioxetine or escitalopram 10–20mg on cognitive function and depression severity in 99 MDD patients with inadequate response to 6 weeks of SSRI or SNRI treatment (Vieta et al., 2018). The DSST was applied as a primary assessment of cognition, with the UCSD Performance-based Skills Assessment-Brief (UPSA-B) used to ascertain functional capacity. Secondary cognition assessments were obtained using the score in Table 4. Although both treatment groups reported improved DSST and UPSA-B performance with no significant differences, improvements in seven cognitive testing domains favoured vortioxetine, with the exception of the TMT-A and SRT. These results again confirm the efficacy of vortioxetine in improving cognitive function and ameliorating depression symptoms, although comparison with escitalopram as an active treatment is difficult without a larger-scale replication trial.

Previous findings regarding ketamine (Shiroma et al., 2014; Yoosefi et al., 2014; Murrough et al., 2015) reported mixed effects on cognition in three small-scale trials, with suggestions that ketamine may improve visual and working memory, potentially due to symptom improvement rather than direct pro-cognitive effects. Extending this research, Chen et al., 2018 trialled doses of 0.2 and 0.5mg/kg of ketamine against placebo saline infusion in 71 patients with TRD (Chen et al., 2018). Using a cognitive battery of two tests (Table 4), they found that, while 0.2mg/kg ketamine did not impair cognitive function, 0.5mg/kg improved attention and response control in a go/no-go task. The negative correlation with depression symptoms may suggest that it was the antidepressant effect that improved cognition.

In conclusion, vortioxetine is a viable antidepressant with cognitive enhancing effects across several domains. More longitudinal replication and active-comparator trials with current first-line therapies, such as SSRIs or SNRIs, are still required, as for ketamine, particularly with a view to developing therapies for the treatment-resistant patients with cognitive deficits. Two ketamine trials are currently undergoing recruitment (ClinicalTrials.gov, NCT02659085; NCT01881763). Further investigation into the pro-cognitive and antidepressant mechanisms of vortioxetine is also important, particularly in acutely depressed patients.

3.4 Evaluation of novel treatments on cognitive impairment

Interest in cognitive therapies has grown considerably over the last two decades. Despite an abundance of exciting opportunities, recent literature has identified numerous limitations, including a lack of standardisation in trial designs, heterogeneous samples, and conflicting results (Carvalho et al., 2014; Bortolato et al., 2014; Sole et al., 2015; Salagre et al., 2017; Miskowiak et al., 2016).

This part of our review will briefly update established findings, evaluate the most recent contributions to the field, and identify potential patient stratification techniques. Although recent reviews of physical, physiological, and biological therapies have been promising, analysis of these interventions is beyond the scope of this review. We refer the reader to studies on deep brain stimulation (Bergfeld et al., 2017; Kubu et al., 2017), repetitive transcranial magnetic stimulation (Noda et al., 2018), transcranial direct current stimulation, (Salehinejad et al., 2017; Martin et al., 2018), cognitive remediation (Bowie et al., 2013; Trapp et al., 2016; Motter et al., 2016), exercise (Brondino et al., 2017; Buschert et al., 2018) and other physical therapies (Greer et al., 2017; Listunova et al., 2018).

Table 5 outlines the main study characteristics for novel therapies used for cognitive impairment in recent trials, generally as augmentation with concomitant antidepressant treatment, and only those with cognitive outcomes have been included.

3.4.1 Stimulants

Stimulants with potential pro-cognitive effects include methylphenidate, modafinil, lisdexamfetamine (LDX), and nicotine (DeBattista et al., 2004; Madhoo et al., 2014; Lavretsky et al., 2015). In a proof-of-concept study, Kaser et al., 2017 (Table 6) reported that modafinil

200mg/day significantly improved episodic and working memory in 60 remitted patients, whereas attention and planning saw no improvement as measured by the CANTAB battery (Kaser et al., 2017). A current placebo-controlled trial of 50 patients should provide further insight into the efficacy of modafinil 200mg/day on cognition in rMDD (NCT03620253).

To our knowledge, no new results have yet been published using methylphenidate and LDX for cognition in MDD. Although LDX augmentation has been of recent interest in MDD, non-significant effects have been reported on depression severity (Richards et al., 2017, Giacobbe et al., 2018). The benefits of LDX may become more apparent when trialled with cognition as a primary outcome, as in a current trial (NCT01148979). McIntyre et al., 2017 has also emphasised targeting psychopathologies such cognitive impairment with stimulants, rather than antidepressant effect (McIntyre et al., 2017b). Although psychostimulants could ameliorate cognitive impairments in MDD, this cannot be confirmed without cognition-specific studies with consistent methodologies, and neuroimaging to confirm target-engagement.

Nicotine, a nicotinic acetylcholine receptor (nAChR) agonist, may have efficacy to improve cognition in MDD. Gandelman et al., 2018 reported mixed effects of nicotine in late-life depression (LLD) in cognitive tests (Gandelman et al., 2018). Where CPT and Rapid Visual Information Processing (RVP) tests were administered, nicotine improved sustained attention. This was not found with the Attention Network Task (ANT), with additional inconsistent results regarding long-term and working memory, potentially mediated via improvements in attention. Currently, a transdermal nicotine 3.5mg-21mg patch is being trialled (NCT02816138). The recommendation of Gandelman et al., 2018 is clear: to conduct a 'randomized, blinded, placebo-controlled trial of transdermal nicotine in non-smokers with LLD', with 'dual outcomes for both depression severity and cognition', with measures to assess 'attentional performance, episodic and working memory, and executive function'. The outcome of this trial will be important for future therapeutic strategies.

3.4.2 Anti-inflammatory and anti-oxidant therapies

Anti-inflammatory and anti-oxidant therapies with potential pro-cognitive effects include S-adenosylmethionine (SAME), omega-3, Erythropoietin (EPO), and metformin.

SAMe is an essential component in human metabolism and biochemistry, including neurotransmitters such as DA, NE and 5-HT (Carvalho et al., 2014). In an augmentation trial of 66 SSRI non-responders with MDD, SAMe 800mg/day showed some positive effects; the subjective CPFQ measure showed improved recall and word finding, but no significant change in any of the other five cognitive domains tested (Levkovitz et al., 2012).

A systematic review by De Berardis et al., 2016 concluded SAMe to be a well-tolerated and potential therapeutic option in MDD and TRD patients (De Berardis et al., 2016). Where those with mild symptoms could benefit from SAMe monotherapy before antidepressant initiation, treatment-resistant populations may also benefit from add-on therapy. More recently, Sarris et al., 2018 conducted an 8-week placebo-controlled RCT in 107 non-remitted MDD patients, where an add-on of 800mg/day SAMe was no superior in effect to placebo (Sarris et al., 2018). No biomarkers significantly correlated with SAMe response. High placebo response and lower dosing of SAMe should, however, be noted in this study, as well as the moderate to severe inclusion criteria. Given that cognitive function has been shown to decline with increasing disease severity, it would be interesting to trial the pro-cognitive ability of SAMe in mildly symptomatic patients, as this could be a key early time-point for future interventions, and an opportunity missed by previous studies.

Omega-3 polyunsaturated fatty acids (PUFAs), including α -linolenic acid, docosahexaenoic acid and eicosapentaenoic acid, have been shown to inhibit the microglial inflammatory response and exhibit a neuroprotective effect in animal models. In 190 MDD patients, supplementation with 1.5g/day n-3 long-chain PUFA led to no significant improvement in cognition (Rogers et al., 2008). In a trial of 36 remitted patients, 2.3g omega-3 fatty acid led to small improvements in emotional decision-making/information processing as measured by the AGN and Facial Expression Recognition task (Antypa et al., 2012). Currently, two trials with cognitive outcome measures are investigating fish oil supplementation in 120 MDD and 89 LLD patients (NCT03295708; NCT01235533).

A 12-week, randomised, placebo-controlled study by Jahangard et al., 2018 investigated omega-3 supplementation alongside sertraline 50-200mg in 50 MDD patients (Jahangard et al., 2018). Using self- and clinician-reported ratings (BDI and MADRS), omega-3 1000mg/day improved symptoms of depression, anxiety, and sleep, as well as emotional

regulation. Generalisability was limited by the small sample size, inclusion of outpatients, and lack of biomarker analysis. In a systematic review of six studies with elderly depressed patients, Bae et al., 2018 concluded that omega-3 fatty acid supplementation was effective in mild-moderately depressed populations, although at a dose higher than 1g/day (Bae & Kim, 2018). In addition, omega-3 fatty acids were linked to increased 5-HT and DA production, as well as reduced oxidative stress and inflammatory cytokine levels.

EPO, a growth factor hormone, increases BDNF production, leading to increased neuroplasticity resulting in a neuroprotective effect to facilitate better cognition (Carvalho et al., 2014). In 19 MDD patients, 3 days of EPO 40,000 IU significantly changed facial recognition response, similar to conventional antidepressant effect (Miskowiak et al., 2010). In 40 TRD MDD patients, the same dose of EPO over 8 weeks led to reduced depression severity and improvement in verbal recall and recognition, measured by RAVLT, in comparison to placebo (Miskowiak et al., 2014).

Ott et al., 2016 performed secondary analysis on a 9-week RCT, in which unipolar (N=36) and bipolar patients (N=43) received EPO 40,000 IU/ml or saline infusions (Ott et al., 2016). EPO improved processing speed in attention, memory, and executive function in both groups (Table 5) an effect maintained at 6-week follow up. Objective, not subjective, baseline cognition predicted greater chance of treatment success in EPO patients, particularly in those with greater verbal memory dysfunction, highlighting the importance of these baseline measures. Li et al., 2018 systematically reviewed four RCTs with adjunctive EPO across affective disorders, including those by Miskowiak et al., 2009, and Miskowiak et al., 2014 in MDD, concluding EPO to have potential pro-cognitive effect (Li et al., 2018). Future studies should aim to overcome heterogeneity in cognitive assessment tools, short study durations, exclusion of patients with relevant co-morbidities such as diabetes mellitus, and lack of functional outcome measures and reporting. Currently, Schmidt et al., 2018 are investigating EPO 40,000IU/ml as an add-on treatment for the cognitive side effects of electroconvulsive therapy (ECT), with the primary outcome a change in composite cognitive score assessing attention, verbal learning, memory, and executive function (Schmidt et al., 2018). Inclusion of structural and fMRI will help explore whether oxidative stress, inflammation, or neuroplasticity biomarkers accompany changes in cognition.

Metformin, indicated for type 2 diabetes mellitus (T2DM), has been linked to hippocampal neurogenesis and improved cognition. In 58 patients with both MDD and T2DM, metformin 1g-2g/day was administered over 24 weeks versus placebo; using the Wechsler Memory Scale, improved cognitive performance was measured across memory, attention, and concentration domains (Guo et al., 2014). To our knowledge, no new trials have yet been published with metformin and cognitive outcomes.

Building on the evidence base for vortioxetine, an RCT conducted by Fourrier et al., 2018 is trialing vortioxetine as an add-on therapy alongside celecoxib 400mg, an anti-inflammatory COX-2 inhibitor, or placebo in 200 MDD patients (Fourrier et al., 2018). Interestingly, the trial will stratify patients into 'Depression with inflammation' and 'Depression without inflammation' groups, with CRP levels >3 mg/L and ≤ 3 mg/L respectively, before randomising patients to celecoxib or placebo over 6 weeks. Patients may opt to continue vortioxetine during a 6-month open-label phase. Cognitive measures will encompass global function, emotional processing and social cognition, using the novel cognitive assessment tool, THINC-it. Biological measures will include CRP, TNF- α , IL-6 and IL-1 β , generating evidence for biomarker stratification of patients for antidepressant treatment, based on inflammatory status.

Moving forward, this personalised approach will be very important to enable greater rates of treatment success and functional recovery in sub-groups of patients. This is especially important for many of the anti-inflammatory therapies reviewed in this section, for which evidence has been overall positive, but relatively sparse.

3.4.3 Opportunities for patient stratification

While it's true that heterogeneity in cognitive assessments and methodology present several problems, it also offers researchers a unique opportunity to individualise therapeutic approaches and maximise benefit provided by potential pro-cognitive agents. The majority of studies investigating anti-inflammatory treatments have classified patients by depression severity or degree of cognitive impairment, using an assortment of scales and batteries. Very few have incorporated biomarker analysis as outcome measures, imaged microglia, or stratified based on inflammatory markers.

Given that the correlation between inflammatory markers such as IL-6 and CRP and depression has been well-documented, this is surprising. Chang et al., 2012 explored whether CRP was significantly associated with depressive symptoms and cognitive impairment in 149 medication-free MDD patients, treated with either fluoxetine 20-80mg or venlafaxine 37.5-75mg over 6 weeks (Chang et al., 2012). Depression severity was measured using HAM-D, and fasting plasma CRP levels measured at baseline and 6 weeks. The neurocognitive battery consisted of the CPT, WCST, and Finger-Tapping Test (FTT). Although no significant link was found between CRP levels and HAM-D score at trial completion, poor psychomotor speed and executive function were significantly associated with higher baseline CRP before treatment. 'Certain patients' with high CRP levels may have enhanced antidepressant response and cognitive improvements, and so targeting these may be the key to treatment success.

Galecki et al., 2018 recently reviewed the anti-inflammatory mechanism of SSRIs and SNRIs. Venlafaxine alleviates renovascular hypertension, reducing endothelial dysfunction, oxidative stress, cholinergic dysfunction and inflammation, which contribute to cognitive impairment (Galecki et al., 2018). Small but significant effects have been reported on activated microglia and to inhibit superoxide generation. SSRIs were found to have neuroprotective, anti-inflammatory, anti-oxidant and anti-apoptotic properties. This is especially interesting given the reported pro-cognitive effects of SNRIs, and the inconsistent results on cognition with SSRIs and SNRIs. Patients with greater baseline inflammation may see greater cognitive improvements, although this is difficult to confirm without blood-based biomarker analysis.

Pariante and colleagues, 2017 have established that not all patients are inflamed to the same degree. Greater inflammation and depression has been recorded in patients exposed to greater childhood stress or maternal depression during foetal neurodevelopment, as well as those with genetic variants pre-disposing them to greater immune response. These genetic variants include G-174C, BanI, and COX2 rs4648308 polymorphisms in the IL-6, cytosolic phospholipase A2 and COX-2 genes respectively (Pariante, 2017). Further molecular analysis has revealed that people with PLA2 and COX2 mutations have reduced endogenous levels of the anti-inflammatory and potential antidepressant mediators, omega-3 fatty acids, docosahexaenoic acids and eicosapentaenoic acids. If genotype can increase depression risk through altered immune response and anti-inflammatory mediators, this will likely determine

how patients respond to treatments such as omega-3 or COX-2 inhibitors like celecoxib, and which patients might be most suitable for these treatments.

Where stratification is performed without biomarkers, inclusion of depressed patients without inflammation in trials may dilute results and facilitate negative and inconclusive findings. In one example, melatonin-SR 3mg has been trialed as an add-on therapy with buspirone 15mg (Targum et al., 2015). CPDQ scores confirmed improved cognition in the augmentation group. Given that Brown et al., 2018 reported that mutations and polymorphisms in genes such as *Per3*, *Cry1*, *Clock* and *Npas2* in MDD may relate to greater degrees of circadian dysfunction, which may in turn affect cognition, these patients with circadian rhythm dysregulation may see far superior benefits with melatonin on cognitive function (Brown et al., 2018). In another study by McGlashan et al., 2018, acute administration of citalopram 30mg correlated with a 47% increase in melatonin suppression, resulting in increased sensitivity to light (McGlashan et al., 2018). These results further indicate that circadian light response is subject to variability and may predict treatment outcomes in certain subsets of patients.

Brown et al., 2018 also highlighted findings where omega-3 treatment response was predicted through inflammatory stratification (Rapaport et al., 2016). Five cytokine biomarkers, IL-1 receptor antagonist (IL-1ra), IL-6, high-sensitivity CRP (hsCRP), leptin and adiponectin, separated patients into 'high' and 'low' grades of inflammation, with 'highly' inflamed patients responding better to eicosapentaenoic acid (EPA) than placebo. Although no overall significant improvements were reported, these findings show that stratification based on inflammatory markers is both feasible and highly relevant to study outcomes.

Anti-inflammatory treatments may have therapeutic benefit in patients with exaggerated reactivity to negative information, somatic symptoms and altered reward processes; surprisingly, the role of inflammatory mechanisms in cognitive control and executive function is not well-evidenced in the literature (Dooley et al., 2018). This may be attributable to lack of sensitivity of neurocognitive batteries to inflammatory changes, although other cognitive domains may be affected more by inflammation, such as learning and memory. Only 33-47% of depressed patients may have high peripheral inflammation, and these are patients most likely to benefit from anti-inflammatory supplements.

Herder et al., 2018 estimated longitudinal associations between diabetes and depression symptoms in 271 individuals with type 1 and 2 diabetes, assessing concentrations of serum hsCRP, IL-6, IL-1ra, IL-18, and CC-chemokine ligand 2 (CCL2) obtained from two RCTs investigating diabetes and depression (Herder et al., 2018). In T2DM, lower concentrations of hsCRP, IL-18 and IL-1RA correlated with reduced depression symptomatology, and increased CCL2 at baseline correlated with reduced symptom improvement. Although trials with metformin and pioglitazone have produced equivocal results, augmentation in comorbid populations with increased inflammatory markers may see greater benefits.

In summary, stratifying certain subsets of patients and targeting anti-inflammatory therapies according to biological marker levels may be a more successful application of novel treatments, and more likely to lead to definitive results. In some cases, this is already underway. Omega-3 is currently being trialled as a personalised approach in 90 and 100 MDD patients with high peripheral inflammation, as well as 60 MDD patients with cardiovascular disease (NCT02553915; NCT03143075; NCT03072823). Applying this individualised treatment approach with other therapies should help overcome inconclusive results and identify treatment pathways for the certain patients who will benefit the most.

4 Discussion

This review evaluated the impact and treatment of cognitive deficits in MDD patients. Despite a wealth of growing knowledge and emerging therapies, current evidence is as yet still equivocal and inconclusive. We posit that there are several key messages for the field to take forward, relating to targeted cognitive interventions, medicines optimisation, patient stratification, and methodological improvements.

1.1 Importance of targeted and timely interventions

Cognitive deficits affect patients in both acute and remitted states, with significant short- and long-term impact on quality of life and functionality (Jaeger et al., 2006; Preiss et al., 2009; Baune et al., 2010; Hasselbalch et al., 2011). Executive function, attention, and memory impairments have been strongly associated with poorer outcomes, with attention

linked to reduced mental and social capabilities. Cognitive deficits do not always present in the same manner, or to the same degree. Increased depression severity correlates with greater magnitude of impairment, and cognition has been found to be worse in first-episode versus multiple-episode patients. Late-onset patients present with more severe dysfunction, particularly in executive function, processing speed, and verbal memory (Bora et al., 2012; Bora et al., 2013).

Importantly, executive function has emerged as the key cognitive domain for psychosocial outcomes, and is the most significant predictor of social cognition, psychosocial, and workplace function for patients in remission. In currently depressed patients, the forward planning subdomain was most associated with overall psychosocial dysfunction, as well as issues with 'autonomy, subjective cognition, and interpersonal relationships'. Cognitive updating was negatively associated with reduced subjective cognition, psychosocial function, and occupational function. Further research into forward planning would be valuable as an indicator of functionality in acute MDD (Knight et al., 2018; Knight & Baune, 2018).

Despite shared diagnoses and clinical similarities, depression patients present with markedly heterogeneous impairments. As early as first-episode, patients have been reported as 'cognitively preserved', or 'cognitively impaired'. 'Cognitively preserved' patients may recover more quickly than their counterparts and require alternative treatment strategies (Vicent-Gil et al., 2018). Although dysfunction could be identified in first-episode patients via hippocampal atrophy, grey matter reduction in the amygdala, and white matter abnormalities, little research has been conducted on whether cognitive impairments appear before diagnosis as in schizophrenia (Lee et al., 2012; Ma et al., 2007). As memory dysfunction has been identified in some 'at risk' individuals, this is also important for future research. Cognitive ability has predicted depression symptom severity at baseline and at 12-month follow-up, with verbal learning, prospective memory, and executive function the strongest predictors of psychosocial functional outcomes at 3- and 6-month follow-up (Cambridge et al., 2018).

A diagnosis of depression is insufficient evidence to confirm either the presence or absence of cognitive impairment (Keilp et al., 2018). Cognitive deficits are often the result of complex interactions at individual and clinical levels, which causes varying degrees of presentation in depressed patients. Timely identification is essential to preserve functional

outcomes (Fig 1). The THINC-it tool is an important step in overcoming previous limitations with exhaustive neurocognitive batteries. The assessment, which can be self-administered by patients or applied by health care professionals, could facilitate detection and relieve long-term complications much earlier (McIntyre et al., 2017a; Cha et al., 2017; Baune et al., 2018).

Given that cognitive impairment can lead to depression relapse, poor prognosis, and reduced employment and workplace productivity, the earlier the detection and prevention of these deficits, the better. Cognitive screening must thus begin at diagnosis. Where cognitive impairments are sooner recognised, they can be sooner treated. As acute and remitted patients display differential executive function, this underscores the importance of early stratification and targeted screening in certain subgroups, such as first-episode patients. An on-going commitment is necessary, and efforts should be made throughout a patient's healthcare journey. This might occur at time-point 3, where adjunct therapy could be administered alongside antidepressant therapy. Additionally, the recruitment of younger patients (<65 years) into research trials at time-point 4 should be considered.

By applying timely, targeted interventions, we can hopefully facilitate earlier identification and improve patient outcomes in both the short- and long-term.

1.2 Optimising therapy in cognitive impairment

Although the case for their treatment is robust, cognitive impairments have yet to be adequately improved by conventional therapies. Antidepressants have presented with varying intra- and inter- class-dependent results, and no single treatment has been found to have consistently superior effects on cognition.

Despite this, some antidepressants may still have better effects on cognition than others. SNRIs have been linked to improved recovery of episodic and working memory (Tian et al., 2016). Given that some studies have not correlated executive control improvements with depression severity, this underscores that SNRIs may exert pro-cognitive effects via mechanisms independent of depression symptom improvement, linked to increased DA concentrations in the frontal, limbic and parietal areas (Herrera-Guzman et al., 2009). More recent evidence has reported that venlafaxine alleviates renovascular hypertension, exhibiting anti-inflammatory

effects linked potentially to cognitive improvement. SSRIs have also been found to have neuroprotective, anti-inflammatory, anti-oxidant and anti-apoptotic capabilities, leading to therapeutic and protective effects (Galecki et al., 2018). This is interesting given reported pro-cognitive effects of SNRIs, and the inconsistent results reported with SSRIs and SNRIs. Patients with greater baseline inflammation may also see greater cognitive improvements with these treatments, although this is difficult to confirm without blood-based biomarker analysis.

Conversely, other antidepressants may have worse effects. TCAs such as dothiepin have been associated with decreased CFF performance, linked to its anticholinergic and antihistaminergic pharmacology (Trick et al., 2004). Adverse side effect profiles may compound existing cognitive difficulties, while sedation could lead to pronounced difficulties with cognitive and psychomotor functions, particularly in elderly populations. For this reason, it may be worth considering switching TCAs for alternative antidepressants in depression patients with significant cognitive impairments.

Vortioxetine is a promising candidate for pro-cognitive therapy. Significant improvements have been reported in processing speed, verbal learning, and recall domains. Additionally, over two-thirds of vortioxetine's effect on cognition is due to direct treatment effect (Katona et al., 2012; Mahableshwarkar et al., 2015; McIntyre et al., 2014; Harrison et al., 2016; Vieta et al., 2018). Ketamine may also improve attention and response control in TRD due to antidepressant effect (Chen et al., 2018).

In terms of novel therapies, several agents have potential. Positive but preliminary findings showed that augmentation with stimulants modafinil, LDX, and nicotine may improve attention, episodic and working memory, and executive function (Kaser et al., 2017; McIntyre et al., 2017b; Gandelman et al., 2018). While the benefits of exercise remain equivocal due to study designs, it is an effective and tolerable add-on therapy (Buschert et al., 2018). Skills training for MDD, similar to Computerised Interactive Remediation of Cognition – a Training for Schizophrenia (CIRCuiTS), could be constructive; if this was accessible, it could have similar positive effects to the 'online homework' used in CR trials (Reeder et al., 2017). Regarding anti-inflammatories, omega-3 supplementation showed improved emotional regulation in mild to moderately depressed patients, and EPO improved processing speed in attention, memory, and executive function (Bae & Kim, 2018; Ott et al., 2016).

Although some therapies have potential pro-cognitive effects, firm conclusions cannot be made until consistent methodologies are employed. We stress that the field urgently requires more large-scale, randomised, placebo-controlled trials, testing cognition as a primary outcome with adequate, ideally standardised, neurocognitive batteries. Until study designs are improved, we are left with a constellation of potential ideas that cannot be fulfilled using current methods. Together with the number of exciting current studies cited earlier in our review, these changes will be of great future importance, and should shed further light on the emerging role of novel agents in cognitive deficit therapy.

1.3 An individualised approach to cognitive impairment

No single population of depression patients is homogenous, and trial participants vary diversely in degrees of depression severity and cognitive impairment. While heterogeneity in cognitive assessments and methodology present us with several problems, these differences offer a unique opportunity to individualise therapies and maximise benefit from pro-cognitive agents. Like cogs that represent distinct functions in machinery, cognition and its domains are highly complex and individual. No one formula can possibly fit all, and therapy may likewise need to reflect this. Certain patient groups are likely to see greater benefit from some therapies more than others, and at different stages of their treatment. By approaching therapy using individual profiles, we may better target impairments using stratified interventions.

This approach is especially important in relation to anti-inflammatory treatments. Since only 33-47% of depressed patients may have high peripheral inflammation, it follows that it is these patients who are most likely to benefit from anti-inflammatory therapies (Dooley et al., 2018). Additionally, if genotype can increase depression risk through altered immune response and increased levels of inflammatory mediators, this could further determine how patients respond to treatments such as omega-3 supplementation, or COX-2 inhibitors such as celecoxib, for which inflamed individuals might be more suitable than others (Fourrier et al., 2018). Stratifying subsets of patients and targeting agents according to biological marker concentrations may be a more successful application of novel treatments and will be more likely to lead to more definitive results.

Cognition in MDD is underpinned by a variety of pathophysiological processes. This complex, multi-faceted picture may be best tackled as a therapeutic profile, where different areas can be modulated (fig 2). At one level, we can review antidepressants and consider augmentation with novel agents. On another, we must individualise therapeutic approaches. We should commit to on-going screening using tools such as THINC-it, and test more rigorously for impairments at trial inclusion. Patient stratification should be improved, i.e. by using 'cognitively preserved' and 'cognitively impaired', or 'depression with inflammation' and 'depression without inflammation', and biomarkers incorporated into study designs (Fourrier et al., 2018; Vicent-Gil et al., 2018). Evidence has underscored that executive function, attention, and memory impairments are most significantly associated with poorer outcomes in MDD patients. These specific domains should therefore be targeted, and further novel therapies and target-engagement mechanisms explored. This framework is supported by positive but preliminary findings, as current evidence is not robust enough to support immediate implementation into practice. Further replication and validation studies are required.

1.4 Methodological limitations and future recommendations

Despite significant regulatory and research advances in recent years, the 'patchwork set of methods' used in studies have all greatly hampered progress (Keefe et al., 2016).

Due to inadequately powered trials and heterogeneous assessments, current results are promising, but remain equivocal. Few studies have measured objective or subjective cognitive deficits at baseline, or tested cognition as a primary outcome. Numerous studies have been inadequate in their detail of medication, including names and doses, and have not always included treatment effect adjustments. Lack of follow-up studies have made valuable longitudinal analysis difficult, particularly with small samples of patients ranging from mild to severely depressed. Most anti-inflammatory studies have classified patients by severity of depression or cognitive impairment, using an assortment of scales and batteries. Very few have incorporated biomarker analysis, imaged microglia, or stratified patients based on inflammatory marker measures.

The assortment of cognitive assessments used has made true comparison difficult. With so many different cognitive tests, the likelihood of methodological inconsistencies is high.

These results not only provide research setbacks, but also confirm the need for standardised neurocognitive measures in MDD, which should be sensitive and accurate enough to detect varying and highly individual degrees of cognitive impairment in depressed patients. A standardised test battery is critical in order to improve future studies, as has already been achieved by MATRICS in schizophrenia.

To overcome limitations and commit to making true advances for patients, we outline five research recommendations (fig 3). First, a standardised cognitive battery should be developed. Second, trial design should include patients below <65 years, with adequate control groups and larger sample sizes. More longitudinal designs, large-scale effectiveness trials and follow-ups would also enable better insight into long-term cognitive effects. Third, sex differences should be researched in greater detail. Despite increased susceptibility to both depression and cognitive impairment, treatment in women with MDD has thus far received inadequate attention. Even though females generally outnumber males in trials, few studies investigated whether differences in cognition may exist, the impact of hormonal status and possible treatment implications. Fourth, patient stratification should take into consideration diverse pathophysiology and aetiology patterns, e.g. immune dysfunction, and target novel therapies accordingly. This should improve target-engagement and delivery to appropriate populations. The addition of more biomarkers and fMRI in study designs would also be ideal. Fifth, we should continue research efforts to validate further novel therapies.

It is important to note that there are limitations of our current review. In order to give a focused assessment of MDD, studies with participants with other diagnoses of depression (bipolar, schizoaffective disorder, etc) were excluded. Use of the PubMed and ScienceDirect search engines may have limited findings to studies only in the public domain, without access to pre-clinical trial data, and may have neglected to identify some studies. Variations in clinical trial designs have also confounded results and made comparisons between studies difficult without standardised practice.

5 Conclusion

Cognitive deficits in MDD are an exciting and important area of research, with valuable recent progress. To ensure future development, four key recommendations are suggested. One, to use THINC-it for earlier detection of cognitive deficits. Two, to develop one unified and standardised cognitive testing battery. Three, to improve clinical trial designs to include more gender analysis, younger patients, longitudinal designs, and patient stratification methods. Four, to continue research efforts to validate therapeutic regimens for cognitive impairment, working towards a 'cognitive profile'. This would enable combinations of antidepressant monotherapy and novel adjuvants to selectively treat different cognitive domains. These developments combined should significantly improve the negative impact of cognitive deficits in patients and overcome the methodological difficulties with on-going research efforts in the field.

6 Conflict of Interest statement

The authors declare that there are no conflicts of interest.

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Table 1. Summary of neurocognitive domains and tests included in cognition studies

Author	Cognitive domains tested	Tests and cognitive tasks used
Jaeger et al., 2006	Attention/Processing speed	D2 errors, Stroop Words, Stroop Colours, TMT Part A, WAIS Digit Symbol Raw
	Working memory	D2 Fluctuation, WAIS Digit Span Forward, LNS Total Correct, LNS Long Term, WAIS Arithmetic Raw, WAIS Digit Span Backward, WMS Logical Memory
	Executive function	WCST Preservatives Errors, COWAT Correct, Animal Naming
	Verbal knowledge	WAIS Vocabulary Raw, WAIS Comprehension raw, WAIS Similarities Raw
	Non-verbal function	WAIS Block Design Raw, WAIS Picture Comprehension Raw, WAIS Picture Arrange Raw
	Motor	WMS Verbal Paired I, II, WMS Visual Paired I, II

	Learning	Finger Tap Preferred, Finger Tap Non-Preferred, Grooved Peg Preferred, Grooved Pref Non-Preferred
Preiss et al., 2009	Memory	AVLT
	Attention and psychomotor speed	TMT Part A
	Executive functions	TMT Part B
Baune et al., 2010	Immediate memory, visuospatial function, language, attention, delayed memory	RBANS
Lee et al., 2012	Psychomotor speed	TMT Part A, Digit Symbol-Coding, Symbol Digit Modalities Test
	Attention	Digit span forwards, spatial span forwards
	Working memory	Digit span backwards; spatial span backwards
	Verbal learning	Logical Memory 1 and 2, RAVLT, Total & Delayed Recall, CVLT-II Total Recall, Short Delayed Free Recall and Long Delayed Free Recall, HVLT Total & Delayed Recall, Buschke's SRT Total Recall
	Visual learning	Visual Reproduction 1 and 2; RCFT 30 Minute Delayed Recall; WMS Visual Memory Index
	Attentional switching	TMT B
	Verbal fluency	Letter and Semantic Fluency
	Cognitive flexibility	WCST, MCST, CANTAB Intradimensional/Extradimensional-Shift (ID/ED)
	Processing speed	Phonetic fluency, semantic fluency
	Verbal memory	List learning, list recall, list recognition

	Executive function	Stroop, TMT part B, Planning, WCST category fluency, WCST preservation
	Working memory	Digit backwards, digit forwards
Rock et al., 2014	Executive function	OTS/SOC, SWM, IED, SSP
	Memory	DMS, PAL, PRM, SRM
	Attention	RVP
	Reaction time	RTI
McIntyre et al., 2017 Cha et al., 2017	Executive function, working memory, processing speed, attention	THINC-it: Spotter Identification Task (Choice Reaction Time), Symbol Check (One-Back Test), Codebreaker (Digit Symbol Substitution Test), TMT Part B, IDN, PDQ-5-D
Vicent-Gil et al., 2018	Executive function	TMT Part B, TOL, WCST, COWAT
	Language	Semantic verbal fluency test, BNT
	Attention and verbal memory	Digit forwards, digit backwards WAIS-III, CPT-II
	Processing speed	DSST, WAIS-III, TMT Part A
	Verbal learning memory	RAVLT

AVLT=Auditory Verbal Learning Test; BNT=Boston Naming Test; CANTAB=Cambridge Neuropsychological Test Automated Battery; CPT-II=Continuous Performance test version II; CVLT-II=California Verbal Learning Test-second edition; COWAT=Controlled Oral Word Association Test; DMS=Delayed Matching to Sample; HVLT=Hopkins Verbal Learning Test; IED=Intra-Extra Dimensional Set Shift; IDN=Identification Task; LNS=Letter-Number Sequencing test; MCST=Modified Card Sorting Test; OTS/SOC=(One Touch) Stockings of Cambridge; PAL=Paired Associates Learning; PDQ-5-D=Perceived Deficits Questionnaire for Depression-5-item; PRM=Pattern Recognition Memory; RBANS= Repeatable Battery for the Assessment of Neuropsychological Status; RCFT=Rey Complex Figure Test; RTI=Reaction Time; RVP=Rapid Visual Information Processing; SRT=Selective Reminding Test; SRM=Spatial Recognition Memory; SSP=Spatial Span; SWM=Spatial Working Memory; TMT=Trail Making Test; TOL=Tower of London; WAIS=Wechsler Adult Intelligence Scale; WCST=Wisconsin Card Sorting Test; WMS=Wechsler Memory Scale.

Table 2. Characteristics of placebo-controlled trials

Author	Treatment groups	Demographics	Depression criteria	Cognitive measures	Outcomes
Raskin et al., 2007	Duloxetine 60mg/day (207) vs PBO (104) 8 weeks	N=311 F: 185 M: 126 Median age: 72 65-90 years	Recurrent MDD DSM IV HAM-D ≥ 18 MMSE	Composite score: 1. Verbal Learning and Recall Test	Duloxetine patients had significantly improved verbal learning and memory. Executive function and attention showed no significant

			≥20	2. Symbol Digit Substitution Test 3. Two-Digit Cancellation Test 4. Letter-Number Sequencing Test	change.
Culang et al., 2009	Citalopram 20-40mg (84) vs PBO (90) 8 weeks	N=174 F: 58 M: 116 Mean age: 79 ≥75 years	DSM IV HAM-D ≥20 Non-psychotic unipolar depression	Composite score: 1. CRT 2. JOLO 3. Stroop test 4. MMSE 5. SRT 6. Digit Symbol Subtest	Citalopram non-responders had worsened learning and psychomotor speed. Citalopram responders had significant improvement in visuospatial functioning and psychomotor speed, but no better than placebo responders.
Reddy et al., 2016	Desvenlafaxine 50mg (52) vs PBO (29) 12 weeks	N=81 F: 52 M: 10 Mean age: 41 18-75 years	MDD MADRS ≥25 Baseline HAM-D 20	Composite scores from CDR tasks: 1. Power of attention 2. Continuity of attention 3. Quality of working memory 4. Speed of working memory TMT A and B Stroop test	Desvenlafaxine significantly improved performance in working memory. No significant difference was reported for attention.
Tian et al., 2016	Venlafaxine 75-150mg (34) vs PBO (30) 6 weeks	N=34 F: 24 M: 10 Mean age: 36	MDD DSM IV MMSE >27	ANT MMSE	Selective improvement in executive control of attention. No improvement reported in alerting deficits.

ANT=Attention Network Test; CDR=Cognitive Drug Research; CRT=Cognitive Reflection Test; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; HAM-D=Hamilton Depression Rating Scale; HRSD=Hamilton Rating Scale for Depression; JOLO=Judgment of Line Orientation; MMSE=Mini-Mental State Examination; PBO=Placebo; SRT=Simple Reaction Time; TMT=Trail Making Test

Table 3. Characteristics of active comparator trials

Author	Treatment groups	Demographics	Depression criteria	Cognitive measures	Outcome
Doraiswamy 2003	Sertraline 50mg (185) vs nortriptyline 25mg (96) or fluoxetine 20mg (105) 12 weeks	N=440 F: 255 M: 185 ≥60 years	MDD DSM III-R HAM-D ≥18	SLT DSST MMSE	Antidepressants improved SLT and DSST performance, but sertraline showed greater improvement in depression severity and cognitive function than nortriptyline or fluoxetine.
Trick et al., 2004	Venlafaxine 75mg (45) or dothiepin 75mg (43) 26 weeks	N=88 F:62 M:26 Mean age: 71 60-83 years	First or new episode MDD DSM IV MADRS ≥19	Composite score: 1. CFF 2. STM 3. CFQ 4. MESS 5. LSEQ 6. ASQ 7. SF36 8. QLDS	Venlafaxine significantly improved CFF scores only. Dothiepin significantly decreased the same measure.
Herrera-Guzman et al., 2009 and 2010	Escitalopram 10mg (26) or duloxetine 60mg (37) 24 weeks, and 24 weeks follow up	N=73 F: 59 M: 14 Mean age: 33 20-50 years	MDD DSM IV HRSD ≥18	CANTAB: 1. WAIS III digit span 2. RAVLT 3. PRM 4. PAL 5. DMS 6. SRM 7. RTI 8. Stroop test	At 24 weeks, both treatments improved episodic memory, with smaller improvements also in working memory, processing speed, and motor performance. Duloxetine

					improved episodic memory more significantly than escitalopram. At 24-week follow up, patients treated with escitalopram had lower verbal and visual memory performance than those on duloxetine.
Culang-Reinleib et al., 2012	Sertraline 50-200mg (33) or nortriptyline 1mg/kg (30) 12 weeks	N=63 F:38 M:25 Mean age: 64	MDD DSM IV HRSD ≥ 16 MMSE ≥ 24	Composite score: 1. MMSE 2. Purdue Pegboard 3. CPT 4. TMT A and B 5. SRT 6. Stroop test	Sertraline patients showed significant improvement in verbal learning, and more so than nortriptyline patients, who reported no improvements.
Soczynska et al., 2014	Bupropion XL 150-300mg (17) or escitalopram 10-20mg (19) 8 weeks	N=38 F:19 M:19 Mean age: 38 18-50 years	MDD HRSD ≥ 16	CVLT-II Wechsler Memory Scale BVM-T-R	Both treatments significantly improved verbal and non-verbal learning and memory, global function, and work productivity.
Gorlyn et al., 2015	Paroxetine 25-50mg (30) or bupropion 150-450mg (27) 8 weeks	N=67 F:30 M:37 Mean age:37	MDD DSM IV HRSD ≥ 16 Prior suicide attempt and/or ideation	CFQ Composite score: 1. SRT 2. CRT 3. TMT A and B 4. WAIS-III 5. BVRT 6. BSRT 7. N-Back 8. COWA	Both treatments improved neurocognitive performance across psychomotor, attention, memory and working memory. Paroxetine had a slightly greater improvement in psychomotor speed.

				T 9. Go-No Go	
Shilyansk y et al., 2016	Escitalopra m 5-20mg (336), or sertraline 12.5- 200mg (336), or venlafaxin e-XR 18.75- 225mg (336) 8 weeks	N=1008 F: 571 M:437 Mean age: 37.8 18-65 years	First onset or recurrent MDD DSM IV HRSD ≥ 17	IntegNeuro battery 1. CPT 2. G-No Go 3. Verbal interfere nce task 4. Austin maze 5. Stroop task 6. Forward digit span 7. CRT 8. TMT A and B 9. Finger tapping	No significant improvements reported in attention, response inhibition, verbal memory, decision speed, or information processing. Where improvements occurred, these were rarely in more than two cognitive domains, and only 4.5% of patients showed any broad cognitive improvements.

ASQ=Ages and Stages Questionnaire; BSRT=Buschke Selective Reminding Test; BVRT=Benton Visual Retention Test; BVMT-R=Brief Visuospatial Memory Test-Revised; CFF=Critical Flicker Fusion; CFQ=Cognitive Failures Questionnaire; COWAT=Controlled Oral Word Association Test; CPT=Continuous Performance test; CVLT-II=California Verbal Learning Test-second edition; DMS=Delayed Matching to Sample; DSST=Digit Symbol Substitution Test; HRSD=Hamilton Rating Scale for Depression; LSEQ= Leeds Sleep Evaluation Questionnaire; MADRS=Montgomery-Åsberg Depression Rating Scale; MESS=Milford-Epworth Sleepiness Scale; MMSE=Mini-Mental State Examination; PAL=Paired Associates Learning; PBO=Placebo; PRM=Pattern Recognition Memory; RTI=Reaction Time; SLT=Shopping List Task; SRM=Spatial Recognition Memory; SRT=Selective Reminding Test; STM=Short Term Memory; SF36=Short Form 36 (SF-36) Health Survey; QLDS=Quality of Life in Depression Scale; RAVLT=Rey Auditory Verbal Learning Test; TMT= Trail Making Test; WAIS-III=Wechsler Adult Intelligence Scale

Table 4: Characteristics for novel antidepressant trials

Author	Treatm ent groups	Demograp hics	Depress ion criteria	Cognitive measures	O ut co m e
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Katona et al., 2012	Vortioxetine 5mg (156) vs duloxetine 60mg (151) vs PBO (145) 8 weeks	N=452 F: 297 M: 155 Mean age: 71 65-88 years	Acute MDD DSM IV MADRS ≥ 26	Composite score: 1. RAVLT 2. DSST	Vortioxetine significantly improved scores testing processing speed, verbal learning and memory, with more direct effects on DSST and RAVLT than duloxetine.
McIntyre et al., 2014	Vortioxetine 10mg (195), 20mg (207) vs PBO (196) 8 weeks	N=598 F:396 M:202 Mean age: 45 18-65 years	Acute MDD DSM IV-TR MADRS ≥ 26	Composite score: 1. DSST 2. RAVLT 3. TMT A and B 4. Stroop Test 5. SRT 6. CRT 7. PDQ 8. MADRS 9. CGI-S	Objective measures reported improvement vs PBO in executive function, attention, processing speed, learning and memory. Subjective measures reported improvement in memory, attention/concentration, and planning/organization
Mahableshwar et al., 2015	Vortioxetine 10-20mg (198) vs duloxetine 60mg (210) vs PBO (194) 8 weeks	N=602 F: 392 M: 210 Mean age: 45 Age range: 18-65	DSM-IV-TR Acute MDD	Composite score: 1. DSST 2. TMT A and B 3. Stroop Test 4. GMLT 5. Detection Task 6. Identification Task 7. One-Back	Significant improvement in DSST and TMT-B, processing speed and executive function Improved PDQ

				Task PDQ CPFQ	
Harrison et al., 2016	Vortioxetine 10mg (200), 20mg (200) vs PBO (200) 8 weeks	N=602 18-65 years	MDD DSM IV	Composite score: 1. DSST 2. RAVLT 3. TMT A and B 4. Stroop Test 5. SRT 6. CRT	Improved cognitive performance in executive function, attention/speed of processing, and memory.
Smith et al., 2018	Vortioxetine 20mg (48) vs PBO (48) 2 weeks	N=96 F: 53 M: 43 Mean age: 35 20-53 years	Remitted MDD DSM IV	Composite score: 1. DSST 2. RAVLT 3. TMT A and B N-back fMRI task PDQ	Vortioxetine reduced neural activity in right dlPFC and left hippocampus, and a network of temporal-parietal areas important for executive function and working memory Improved TMT performance
Vieta et al., 2018	Vortioxetine 10-20 mg (50) or escitalopram 10-20 mg (49) 8 weeks	N=99 F: 74 M: 25 Mean age: 48 18-65 years	MDD DSM-IV-TR Inadequate response to 6 weeks of SSRI or SNRI treatment MADRS ≥ 26 PHQ-9 ≥ 14 PDQ-D ≥ 25	UPSA-B PDQ-D Composite score: 1. DSST 2. TMT A and B 3. SRT 4. CRT 5. RAVLT 6. Stroop Test	DSST and UPSA-B performance improved in both groups. Improvements in seven domains favoured vortioxetine, with the exception of TMT-A and SRT.
Chen et al.,	0.2mg/kg	N=71	DSM-IV	Working memory	0.2mg/kg

2018	ketamine (23), 0.5mg/kg ketamine (24), or PBO normal saline (24)	F: 53 M: 18 Mean age: 47.35 21-65 years	TRD HDRS 23	task Go/No-Go Task	ketamine did not impair cognitive function. 0.5mg/kg ketamine improved attention and response control in go/no-go task performance, with negative correlation with depression symptoms suggesting this antidepressant effect improved cognition.
	2 weeks				

CGI-S=Clinical Global Impression–Severity scale; CPFQ= Cognitive and Physical Functioning Questionnaire; CRT=Cognitive Reflection Test; DSST=Digit Symbol Substitution Test; EWPS=Endicott Work Productivity Scale; GMLT=Groton Maze Learning Test; MADRS=Montgomery-Åsberg Depression Rating Scale; RAVLT=Rey Auditory Verbal Learning Test; SRT=Selective Reminding Test; PBO=Placebo; PDQ= Perceived Deficits Questionnaire; TMT= Trail Making Test; UPSA-B=UCSD Performance-Based Skills Assessment; WLQ-25=The Work Limitations Questionnaire

Table 5 – Characteristics for novel therapies with cognitive outcomes

Treatment	Author or groups	Treatment groups	Demographics	Depression criteria	Cognitive measures	Outcomes
Modafinil	Kaser et al., 2017	Modafinil 200mg/day (30) or PBO (30)	N=60 F: 37 M: 23 Mean age: 45.03 18-65 years	ICD-10 unipolar depression in remission MADRS <12	CANTAB 2. RVP 3. SOC 4. SWM 5. PAL	Modafinil lead to significant improvement in episodic memory and working memory domains, but not in attention or planning.

Erythropoietin (EPO)	Ott et al., 2016	8-weekly EPO 40,000 IU/ml (40) or saline NaCl 0.9% infusions (39)	N=79 F: 55 M: 24 Mean age: 42	N=36 with UD N=43 with BD HDRS ≥ 17 TRAQ	RAVLT RBANS WAIS-III TMT-B RVP CPFQ	EPO improved processing speed in attention, memory, and executive function in both groups, which was maintained at 6-week follow up.
		9 weeks				

CPFQ= Cognitive and Physical Functioning Questionnaire; PAL= Paired Associates Learning; RVP= Rapid Visual Information Processing; SOC=Stockings of Cambridge; SWM=Spatial Working Memory; TMT=Trail Making Test; WCST=Wisconsin Card Sorting Test; WMS-III=Wechsler Memory Scale; WAIS-III=Wechsler Adult Intelligence Scale; VLMT=Verbal Learning and Memory Test; VRMD= Verbal recognition memory – delayed; VRMI=Verbal recognition memory – immediate.

Figure 1

Figure 2

Figure 3