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Title: Putative neuroprotective pharmacotherapies to target the staged progression of mental illness

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Abstract

Objective: Neuropsychiatric disorders including depression, bipolar and schizophrenia frequently exhibit a neuroprogressive course from prodrome to chronicity. There are a range of agents exhibiting capacity to attenuate biological mechanisms associated with neuroprogression. This review will update the evidence for putative neuroprotective agents including clinical efficacy, mechanisms of action and limitations in current assessment tools, and identify novel agents with neuroprotective potential.

Method: Data for this review were sourced from online databases PUBMED, Embase and Web of Science. Only data published since 2012 was included in this review, no data was excluded based on language or publication origin.

Results: Each of the agents reviewed inhibit one or multiple pathways of neuroprogression including: inflammatory gene expression and cytokine release, oxidative and nitrosative stress, mitochondrial dysfunction, neurotrophin dysregulation and apoptotic signalling. Some demonstrate clinical efficacy in preventing neural damage or loss, relapse or cognitive/functional decline. Agents include: the psychotropic medications lithium, atypical-antipsychotics and antidepressants; other pharmacological agents such as minocycline, aspirin, cyclooxygenase-2 inhibitors, statins, ketamine and alpha-2-delta ligands; and others such as erythropoietin, oestrogen, leptin, N-acetylcysteine, curcumin, melatonin and ebselen.

Conclusions: Signals of evidence of clinical neuroprotection is evident for a number of candidate agents. Adjunctive use of multiple agents may present a viable avenue to clinical realisation of neuroprotection. Definitive prospective studies of neuroprotection with multimodal assessment tools are required.

Abbreviations

5HT - Serotonin

AA – Arachidonic acid

Akt – Protein Kinase B

AMPK - Adenosine monophosphate activated protein kinase

ADNP - Activity dependent neuroprotective protein

BAD – Bcl-2-associated death promoter

Bcl-2 – B-cell lymphoma 2

BDNF – Brain Derived Neurotrophic Factor

BrdU - 5-bromo-2'-deoxyuridine

cAMP - Cyclic adenosine monophosphate

CA – Cornu Ammonis

CaMKII - Ca^{2+} Calmodulin dependent protein kinase II

COX – Cyclooxygenase

DHA - Docosahexaenoic acid

EPA - Eicosapentaenoic acid

ERK1/2 – Extracellular Signal Regulated Kinases

GSK-3β - Glycogen synthase kinase 3 beta

GPR30 - G-protein couple receptor 30

IL – Interleukin

IMPase - Inositol monophosphatase

INFα - Interferon alpha

MRI – Magnetic Resonance Imaging

MT_1/MT_2 – Melatonin receptors 1 and 2

mTOR – Mechanistic target of rapamycin

NMDA - N-methyl-D-aspartate

NRF2 - Nuclear transcription factor (erythroid-derived 2)-like 2

NAC – N-acetylcysteine

PET – Positron emission tomography

PGE_2 – Prostaglandin E_2

PI3K - Phosphoinositide 3 kinase

PKA – Protein kinase A

ROS – Reactive oxygen species

SIR – Social isolation rearing

Th1/2 – T-helper cell 1 and 2

TNF – Tumour Necrosis Factor

TRYCAT – Tryptophan catabolite

VBM – Voxel based morphometry

Introduction

Neuropsychiatric disorders including depression, bipolar and schizophrenia manifest a trajectory and course that frequently but not invariably encompasses a prodromal phase, first episode, recurrence and potential chronicity. Beginning even earlier than the prodrome, a cascade of disease processes may begin and lead ultimately to neurostructural and consequent functional changes. This may leave sufferers more vulnerable to relapse, less responsive to treatment and burdened with cognitive impairment and functional decline.

Neuroprogression is a theoretical construct which defines the underpinning elements of this process, characterised by cumulative insults to the brain over a lifetime of neuropsychiatric disease. Neurostructural abnormalities may represent the apex of neuroprogression with multiple convergent pathways contributing to this including: immune challenges, risk genes, inflammation, oxidative stress and mitochondrial dysfunction.

Neurostructural abnormalities

The most tangible evidence for neuroprogressive changes are the alterations of brain structure associated with neuropsychiatric disease. The advent of magnetic resonance imaging (MRI) derived voxel-based morphometry (VBM) has allowed comprehensive analysis of this phenomenon. In first-episode schizophrenia, cortical volume loss is most predictably seen in the anterior cingulate cortex (Brugger & Howes, 2017), while in treatment-resistant schizophrenia the left middle frontal, right precentral and right middle temporal gyri lose cortical volume (Mouchlianitis, McCutcheon, & Howes, 2016). Mood

disorders are associated with complex patterns of grey matter loss. A recent meta-analysis of depression (n=4101) and bipolar disorder (n=2407) showed both conditions are associated with grey matter loss in dorsomedial and ventromedial prefrontal cortex, including the anterior cingulate cortex and bilateral insula (Wise et al., 2017). However, depression was more strongly associated with grey matter loss in the right dorsolateral prefrontal cortex and left hippocampus, as well as, cerebellar, temporal and parietal regions.

White matter volume and integrity, assessed with MRI based diffusion tensor imaging, is also compromised in diverse neuropsychiatric disorders. Regarding overall white matter volume in schizophrenia, findings are inconsistent with studies showing both loss and gain of volume; however, disrupted fibre tract integrity appears to be a consistent feature (Mouchlianitis et al., 2016). In depression and bipolar disorder, white matter integrity is consistently impaired in the genu of the corpus callosum and posterior cingulum fibres (Dong et al., 2017).

The gross neurostructural changes mentioned above may represent the apex of neuroprogression resulting from an imbalance between neurogenesis and neurodegeneration – an imbalance to which dysregulation of neurotrophins may directly contribute. Serum levels of brain derived neurotrophic factor (BDNF), the most commonly assayed neurotrophin, are reduced in patients suffering from bipolar disorder (Munkholm, Vinberg, & Kessing, 2016). Furthermore, a small post-mortem analysis of brain tissue from elderly patients with major depression suggests BDNF and neurotrophin 3 (NT3) are reduced compared to healthy controls (Sheldrick, Camara, Ilieva, Riederer, & Michel, 2017). In schizophrenia, peripheral BDNF levels are lower compared to controls but BDNF levels do not correlate with disease severity (Fernandes et al., 2015). Animal models of neuropsychiatric disease demonstrate aberrant neurotrophin levels, which have been associated with local upregulation of pro-apoptotic pathways such as the B-cell

lymphoma 2 (Bcl2)/Bcl2-associated X protein (Bax)/Caspase 3 pathway; representing an environment favouring neurodegeneration and associated neurostructural abnormalities (Nowakowska, Kus, Ratajczak, Cichocki, & Wozniak, 2014; G. Reus et al., 2012). Directly influencing neurostructural integrity, these pathways are likely triggered by unchecked inflammation as well as redox stress upstream.

Immune challenges, risk genes and inflammation

In the case of schizophrenia, immune challenges in utero may be the first hit in the life course of inflammatory reactions (Davis, Moylan, Harvey, Maes, & Berk, 2014). First hits include seasonality of birth, obstetric complications, maternal infections or metabolic disturbances, which could influence gene expression leading to inflammation and abnormal development. When combined with further hits like trauma and unfavourable lifestyle factors, an increased inflammatory set point may be propagated into later life. This hypothesis was supported in a multicentre epigenome wide analysis of schizophrenic patients versus controls (n=1714) (Hannon et al., 2016). This study identified clusters of DNA methylation, indicating altered gene expression, in regions coding for immunity and neuroplasticity/neurodevelopment.

Meta-analysis of 68-studies provides further evidence for the role of inflammation in mental illnesses (Goldsmith, Rapaport, & Miller, 2016). They demonstrated peripheral inflammatory cytokines interleukin-6 (IL-6) and tumour necrosis factor alpha (TNFα), as well as, soluble cytokine receptor (sIL-2R) and cytokine antagonist (IL-1RA) are significantly increased during acute exacerbations of adult schizophrenia, bipolar disorder and depression; IL-6 is increased in chronically ill patients of all three

conditions; and IL-β and sIL-2R seem elevated only in patients with chronic schizophrenia and euthymic bipolar disorder.

This milieu of circulating inflammatory cytokines may activate and then be propagated by cellular immunity. A small human blood sample (n=60) identified low T-helper cell 1 (Th1)/Th2 ratio and preferential differentiation of macrophages to the pro-inflammatory M1 phenotype in bipolar disorder but not schizophrenia (Brambilla et al., 2014). Others have suggested schizophrenia may be related to irregular Th1/Th2 signalling, though further work is required to confirm this (Davis et al., 2014). Positron emission tomography (PET) imaging can be used to assess activation of microglia, the macrophages of the brain, as a measure of cellular immune activation. In schizophrenia, studies are conflicted with some showing microglial over-activation in the patients with established disease and those at ultra-high risk of psychosis (Selvaraj et al., 2017); however, others suggest microglia are normal or even under active at similar stages of disease (Di Biase et al., 2017; Holmes et al., 2016). Microglia were shown to be over-active in major depression (Holmes et al., 2017). This was associated with cortical volume loss suggesting a relationship between chronic inflammatory states and neuroprogression.

Adding to this positive feedback loop of inflammatory consequences is abnormal tryptophan metabolism. Tryptophan is the essential pre-cursor for serotonin. Intermediates in the tryptophan pathway known as tryptophan catabolites (TRYCATs) are either pro-inflammatory and neurotoxic or anti-inflammatory and neuroprotective (Morris, Carvalho, Anderson, Galecki, & Maes, 2016). Pro-inflammatory and neurotoxic TRYCATs include quinolinic acid (QA) and 3OH-kynurenine (3HK) which are over-produced in an inflammatory milieu such as is seen in depression and schizophrenia, correlating with worsening of negative symptoms including cognition (Kanchanatawan et al., 2017).

Oxidative stress and mitochondrial dysfunction

The activation of immune-inflammatory pathways is tightly linked to oxidative and nitrosative stress (O&NS) and lowered antioxidant defences. Circulating cytokines, macrophage activity and TRYCATs contribute to reactive oxygen species (ROS) and reactive nitrogen species (RNS) production culminating in cellular damage and possibly neuroprogression (Moylan et al., 2014). Meta-analysis of medication naïve depressed patients showed increased oxidative stress with raised malondialdehyde and reduced antioxidant uric acid levels (Jimenez-Fernandez et al., 2015). In bipolar disorder, there is similarly increased lipid peroxidation, DNA/RNA damage and nitric oxide levels (N. C. Brown, Andreazza, & Young, 2014). In schizophrenia, antioxidant defences are weakened, as indicated by decreased super oxide dismutase (Flatow, Buckley, & Miller, 2013). Finally, reduced peripheral glutathione levels, a master anti-oxidant, are associated with symptom severity in bipolar disorder and schizophrenia (Nucifora et al., 2017). Heavily reliant on natural antioxidant defences, mitochondria can become dysfunctional in disease states producing excess ROS and contributing to the inflammatory cycle (Morris & Maes, 2014). Mitochondrial dysfunction has been implicated in all three neuropsychiatric conditions (Hjelm et al., 2015; Kasahara & Kato, 2017).

In summary, the above-mentioned processes outline the key elements of neuroprogression. Attenuation of these processes is the aim of neuroprotection via agents that target the operative pathway elements. This paper aims to identify agents with neuroprotective potential in neuropsychiatric disorders and review evidence for these agents including clinical efficacy, mechanisms of action and limitations in our current assessment tools.

Method

Data for this review were sourced from online databases PUBMED, Embase and Web of Science. A Boolean search was carried out in October 2017 with no language or publication origin restriction using search terms consistent with those provided in supplementary material. Only data published since 2012 was included in this review.

1. Psychotropic Agents

1.1 Lithium

Lithium has received more clinical assessment of its neuroprotective capacity than any other agent, most notably in bipolar disorder. Cross-sectional studies of bipolar patients have associated lithium treatment with: 1) attenuation of cortical grey matter loss and 2) maintained white matter integrity (**Table 1: Psychotropic Agents**) (Giakoumatos et al., 2015; Gildengers et al., 2015; Hajek et al., 2014; Hajek et al., 2012; Hartberg et al., 2015; Pfennig et al., 2014; Poletti, Locatelli, Radaelli, Colombo, & Benedetti, 2014; Simonetti et al., 2016; van Erp et al., 2012; Zung et al., 2016). Though few have correlated lithium's structural benefits with a similar improvement in brain function.

MRI studies implicate the hippocampus, among other regions, as an area susceptible to cortical atrophy in bipolar with particular relevance to cognition and mood dysregulation (Giakoumatos et al., 2015; Hajek et al., 2014; Simonetti et al., 2016; van Erp et al., 2012; Zung et al., 2016). Three of these studies identify

hippocampal subfields cornu ammonis (CA)1, CA2/3, CA4/dentate gyrus, presubiculum and subiculum as being preferentially affected (Giakoumatos et al., 2015; Simonetti et al., 2016; van Erp et al., 2012). In these studies, lithium treatment was associated with ameliorated bipolar disorder associated cortical atrophy, restoring the volume of the hippocampus and other affected regions to the level of healthy controls. Furthermore, chronicity of lithium treatment is positively associated with the maintenance of cortical thickness (Giakoumatos et al., 2015; Hajek et al., 2014; Hartberg et al., 2015; Poletti et al., 2014; Simonetti et al., 2016; van Erp et al., 2012; Zung et al., 2016). This occurs without global increase in cortical thickness, suggesting lithium's neuroprotective qualities may be targeted at disease affected areas only. This is important as the reliability of MRI in the setting of lithium therapy has been questioned. A study of healthy human subjects (n=12) suggested lithium treatment alters grey matter T_1 relaxation time to produce a false positive reading of global cortical hypertrophy when assessed via VBM (Cousins, Aribisala, Ferrier, & Blamire, 2013). As lithium appears to prevent atrophy with specificity to bipolar disorder affected regions, the probability of this being artefact, which would occur globally, is low.

In addition to cortical grey matter atrophy, poor white matter integrity may be a feature of neuroprogression in bipolar disorder (Berk et al., 2017; Gildengers et al., 2015). MRI based comparison of elderly patients with bipolar disorder (n=58) and age matched controls (n=21) demonstrated that bipolar disorder patients had poorer white matter integrity (M. F. Kraus et al., 2007). Lithium treated bipolar patients (n=33) had better white matter integrity than those not on lithium (n=27). Additionally, duration of lithium therapy had a positive association with white matter integrity. In the only available prospective clinical trial of lithium with neuroprotection as a primary outcome, lithium was shown to preserve white matter volume in the left internal capsule following a first episode of mania (Berk et al., 2017). First episode mania patients were treated with either lithium (n=20) or quetiapine (n=19) monotherapy for a period of twelve-months and brain structure was assessed by MRI at baseline, three-

months and twelve-months. Quetiapine, unlike lithium, did not impact structural brain change in this time-frame (Berk et al., 2017). In this same cohort of patients, early lithium treatment was associated with preserved verbal fluency, a marker of preserved cognition (Daglas et al., 2016). However, this connection between improved brain structure and function has proven elusive to other studies.

Despite lithium showing more capacity for maintaining neurostructural integrity than other agents in bipolar, there is only sparse evidence connecting this with superior functional outcomes. Increased grey matter volume was not associated with fewer symptoms of mania or depression at the time of assessment (Hartberg et al., 2015), reduced rates of relapse when looked at retrospectively (Hajek et al., 2014) nor improved cognition compared to bipolar disorder patients on other agents (Giakoumatos et al., 2015). Improved white matter integrity seen with lithium therapy was not associated with improved cognition in elderly bipolar disorder patients (Gildengers et al., 2015). In one of the few studies assessing lithium's effect on cognition as a primary outcome, Pfennig et al. (2014) compared euthymic bipolar disorder patients managed on either lithium (n=58) or other agents (n=31) and healthy controls (n=53). The single significant difference in cognition between bipolar disorder patients and healthy controls was slower early visual processing, a measure of information processing speed. Lithium correlated with significantly slower early visual processing than other treatments. Whether this represents an adverse effect of lithium, or poorer attenuation of functional decline is unclear. Furthermore, as the subjects were middle aged (mean age=47 years), it may be that bipolar disorder associated cognitive deficit has not yet presented itself, therefore, confounding interpretation of this work.

Mechanistically, lithium may reduce the oxidative stress burden seen in bipolar disorder (De Sousa, Zanetti, Talib, Gattaz, & Machado-Vieira, 2013; de Sousa et al., 2014). Furthermore, rat studies suggest lithium abrogates inflammatory signalling pathways including those associated with toll-like receptor 4

(TLR4) (Khan et al., 2017). Lithium inhibition of TLR4 may reduce phosphorylation of nuclear factor-κB (NFκB) to suppress inflammatory gene expression, quieten microglial activity and inhibit neuronal apoptosis indicated by decreased caspase-3. Lithium may also have a neurotrophic effect by increasing hippocampal BDNF in the setting of a neurotoxic insult (Motaghinejad, Seyedjavadein, Motevalian, & Asadi, 2016) - a finding replicated in rat hippocampal neurons *in vitro* (Dwivedi & Zhang, 2014).

1.2 Second-generation antipsychotics and neurostructural integrity

A meta-analysis of 317 studies and over 9000 patients demonstrated a 2.6% reduction in total brain volume in patients with schizophrenia versus healthy controls (Haijma et al., 2013). Total grey matter loss was most pronounced in those on high dose second-generation antipsychotics at the time of scanning. In isolation, this finding would suggest a correlation between second-generation antipsychotic treatment and brain atrophy. However, antipsychotic therapy is standard across the disorder and may be a marker rather than a mediator; grey matter loss was also associated with duration of illness. Antipsychotic naïve patients had a substantially lower duration of illness than their treated counterparts. This hinders the interpretability of the effect of antipsychotic use on brain volumes. It cannot be definitively ascertained whether the atrophy observed represents: 1) natural disease progression with no effect from antipsychotics, 2) slowed progression due to neuroprotection from antipsychotics, or 3) accelerated progression due to neurotoxicity from antipsychotics. A more recent meta-analysis suggests that antipsychotic exposure is associated with greater volume loss independent of duration of illness (Fusar-Poli et al., 2013). However, this group did not differentiate between early and second-generation antipsychotics. A third meta-analysis found that early antipsychotics accelerate loss of grey matter while

second-generation antipsychotics attenuate this loss in a dose dependent manner (Vita, De Peri, Deste, Barlati, & Sacchetti, 2015).

In summary, without well-powered prospective clinical studies with appropriate control groups, it is difficult to ascertain with relative certainty, whether antipsychotics potentiate or attenuate cortical volume loss.

1.2.1 Clozapine

Robust human data relating clozapine with neuroprotection is limited. In a two-study series, it was suggested clozapine does not slow grey matter atrophy or loss of white matter integrity in treatment resistant schizophrenic patients; despite universal clinical improvement (Ahmed et al., 2015; Forde et al., 2012). However, these studies compared treatment resistant schizophrenic patients on clozapine (n=33 and n=21 respectively) to age matched healthy controls (n=31 and n=21 respectively) without a third group of antipsychotic naïve patients or patients on other therapies; making interpretation problematic.

Clozapine is thought to induce neurogenesis; proliferation of 5-bromo-2'-deoxyuridine (BrdU) positive cells (labelled putative neurons) in the hippocampus of healthy mice treated with clozapine is indicative of this effect (Chikama et al., 2017). This neurotrophic action is likely occurring through increased expression of BDNF in the hippocampus of clozapine treated mice (Gumuslu et al., 2015; H.-W. Kim, Cheon, Modi, Rapoport, & Rao, 2012). This is a poignant finding as serum levels of BDNF are decreased in antipsychotic naïve schizophrenic patients and increased in clozapine responders (Krivoy et al., 2017; Toll & Mane, 2015). Importantly, clozapine induced neuroproliferation is organised and functional. In a chronic mild stress model of depression in mice, clozapine restored neuronal architecture in the dentate

gyrus with dendritic length equalling that of healthy controls (Morais et al., 2017). Furthermore, neuron cell survival was significantly increased with clozapine.

The anti-inflammatory properties of clozapine highlight its potential for neuroprotection. The brains of clozapine treated rats exhibited preferential throughput of the anti-inflammatory docosahexaenoic acid (DHA) cascade over the pro-inflammatory arachidonic acid (AA) cascade (H.-W. Kim et al., 2012). As evidenced by increased DHA protein levels, decreased cyclooxygenase (COX) activity and lower concentrations of prostaglandin E_2 (PGE_2), a pro-inflammatory AA metabolite. Additionally, Clozapine both alone and in combination with N-acetylcysteine (NAC) normalises tryptophan metabolism, diverting away from production of neurotoxic TRYCAT QA in social isolation reared (SIR) rats – a rat model of schizophrenia (Moller, Du Preez, Emsley, & Harvey, 2012; Moller et al., 2013; Moller, Du Preez, Viljoen, Berk, & Harvey, 2014).

1.2.2 Aripiprazole

There is a preliminary body of evidence for aripiprazole in neuroprotection. Aripiprazole has been shown to raise plasma BDNF in patients (n=50) following first episode psychosis (Yoshimura et al., 2012). Chronic aripiprazole increases hippocampal levels of BDNF and ameliorates cognitive deficit in prenatally stressed rats (Nowakowska et al., 2014). A cross-sectional study of schizophrenic patients (n=101) compared the cognitive impact of olanzapine, risperidone and aripiprazole (Hori et al., 2012). Only aripiprazole was found to have a neutral impact on cognition, while other agents were associated with cognitive decline. Using N-methyl-D-aspartate (NMDA) receptor blockade in rats as a model of schizophrenia, Deiana et al. (2015) showed aripiprazole is superior to olanzapine and risperidone when rescuing cognition.

Collectively these studies do not address mechanistic pathways in detail. Considering aripiprazole's differing receptor affinity to most second-generation antipsychotics which includes partial agonism of dopamine (D2) and serotonin ($5HT_{1A}$) receptors, studies investigating the mechanisms by which these differences may influence the neuroprotective potential of aripiprazole would be valuable.

1.2.3 Olanzapine

Olanzapine did not increase plasma BDNF in a 6-week prospective study of schizophrenic patients (n=50) (Kudlek Mikulic et al., 2017). A study of ethnically homogenous schizophrenic patients correlated olanzapine treatment with shortened leukocyte telomere length and advanced metabolic age (Monroy-Jaramillo et al., 2017). Furthermore, olanzapine therapy in rats is associated with raised circulating inflammatory cytokines. Elevated TNFα, IL1β and IL6 were found in the hypothalamus (a structure lacking a blood brain barrier) and adipose tissue of rats treated with olanzapine (Q. Zhang, He, Deng, Wang, & Huang, 2014). Whether this peripheral promotion of inflammation from olanzapine leads to central neurotoxicity is unclear, though the animal studies described below would suggest not.

Olanzapine up-regulates cellular survival pathways in the pre-frontal cortex, hippocampus and striatum of rats (G. Reus et al., 2012). Specifically, olanzapine had a dose dependent preference for increasing expression of BDNF and Bcl-2 over Bcl-2 associated death promoter (BAD) expression, or, neurogenic and anti-apoptotic over pro-apoptotic pathways. These effects were enhanced when combined with fluoxetine. Like aripiprazole, olanzapine improves cognition and increases hippocampal BDNF in prenatally stressed rats (Nowakowska et al., 2014). In light of these neuroprotective qualities of

olanzapine, strategies to mitigate olanzapine's peripheral toxicity would themselves be of neuroprotective benefit.

1.2.4 Risperidone and paliperidone

A study of antipsychotic naïve first episode psychosis patients (n=51) found 12-weeks of risperidone correlates with reduced oxidative stress in the periphery, irrespective of clinical response (Noto et al., 2015). Unlike olanzapine, evidence suggests risperidone's peripheral anti-inflammatory actions may correlate directly with central effects. Risperidone upregulates Bcl-2 expression and BDNF in the brain of SIR rats (Yang, Yang, Wan, Huang, & Liu, 2017). Risperidone prevents the neuropathological changes seen in the offspring born to dams subjected to maternal immune activation, which is a well validated preclinical model of schizophrenia (Piontkewitz et al., 2013). These neuropathological changes include impaired neurogenesis, disturbed micro-vascularisation and loss of parvalbumin expressing hippocampal interneurons (associated with pathogenesis of schizophrenia). Paliperidone has also prevented changes induced by maternal immune activation though in mice (MacDowell et al., 2017). In this model, paliperidone had a net antioxidant effect through at least two mechanisms: 1) upregulation of nuclear transcription factor (erythroid-derived 2)-like 2 (NRF2), which drives antioxidant gene expression and 2) polarization of microglia to their antioxidant phenotype M2. Paliperidone decreases activity of antioxidant enzymes adenosine deaminase, xanthine oxidase and catalase in rat brain tissue indicating reduced burden of oxidative stress (Demirci et al., 2015).

1.2.5 Quetiapine

Efficacious in mood disorders and psychosis, quetiapine has a mixed body of evidence relating to neuroprotection. In a prospective clinical trial of quetiapine versus lithium following first episode of mania, quetiapine was inferior to lithium in preserving white matter volume (Berk et al., 2017). However, quetiapine was efficacious against cuprizone induced demyelination and schizophrenia like behaviour in mice (Wang et al., 2016; Y. Zhang et al., 2012). Quetiapine rescued demyelination with associated stimulation of notch signalling, a regulator of oligodendrocyte maturation and myelination. Protection of myelin may also occur through inhibition of microglia via normalising intracellular Ca^{2+} homeostasis (H. Wang et al., 2015).

Quetiapine may also be an effective antioxidant. Across two studies in mice, acute and chronic quetiapine increased mitochondrial respiratory chain activity and reduced markers of oxidative stress in the pre-frontal cortex, nucleus accumbens, amygdala and hippocampus (Ignácio et al., 2017; Ignacio et al., 2015).

→ **Table 1: Psychotropic Agents**

1.3 Antidepressants

The roles of specific antidepressants - selective serotonin re-uptake inhibitors (SSRIs), selective serotonin noradrenaline re-uptake inhibitors (SNRIs), tricyclic antidepressants (TCAs) and others - in neuroprotection is a discussion that warrants its own review. Therefore, the central theories of antidepressant driven neuroprotection, as well as, emerging evidence will be discussed here.

A recent systematic review and meta-analysis of depressed patients (n=2384 antidepressant free patients and n=1249 antidepressant treated patients) versus healthy controls (n=2982) suggests antidepressant

treatment rectifies deficits in peripheral BDNF (Molendijk et al., 2014); possibly as a secondary result of central neurogenesis (Sachs & Caron, 2014). Antidepressants have been shown to alter mitochondrial function, increase mitochondrial biogenesis and enhance capacity for dealing with oxidative stress in animal models of depression (Demirda_, Nazlıro lu, & Övey 0, 2017; Glombik et al., 2017; Villa et al., 2017). A meta-analysis (n=1137 total subjects) shows antidepressant therapy correlates with a net decrease in peripheral inflammatory cytokines (Wiedłocha et al., 2017). Specifically, antidepressant therapy decreased IL-4, IL-6, IL-10 and IL-β. Though evidence of this correlating with central anti-inflammatory effects is scarce. Duloxetine has been shown to suppress pro-inflammatory cytokines in the hippocampus of adolescent rats (X. Zhang et al., 2016). Sertraline prevents induction of IL-β and TNF-α by seizure activity in the rat hippocampus (Sitges, Gómez, & Aldana, 2014). Antidepressants may augment the TRYCAT pathway to favour neuroprotective conditions. A study of patients with depression exhibits increased production of neurotoxic TRYCATs and subsequent reduction with escitalopram treatment (Halaris et al., 2012). These pathways represent multiple convergent mechanisms thought to be neuroprotective, though emerging evidence suggests the actions of antidepressants may be context dependent and therefore more difficult to elucidate than previously thought.

Antidepressants, in particular SSRIs, may increase neural plasticity and therefore induce undirected susceptibility to change. Meaning the SSRI treated brain is hyper-responsive to environmental influence. In an environment that promotes recovery, SSRI treatment may prime the brain to adopt the positive neurostructural changes leading ultimately to an improved mental state. However, in an environment promoting mental illness, SSRIs may propagate further maladaptive changes leading to a worsened mental state. Across two studies, previously stressed mice (24-days of stress) treated with fluoxetine in an enriched environment (21-days of treatment) exhibit lower levels of anhedonia, dramatically increased hippocampal and hypothalamic BDNF and lower plasma corticosterone levels to vehicle treated mice

(Alboni et al., 2017; Branchi et al., 2013). However, fluoxetine treatment in a stressed environment exacerbates the depressed phenotype, reduces hippocampal and hypothalamic BDNF, slows hippocampal proliferation and increases plasma corticosterone. In a third study of similar design, the effects of fluoxetine on inflammatory cytokines and microglial function were also dependent on environmental conditions (Alboni et al., 2016). Paradoxically in the enriched environment, fluoxetine increases hippocampal expression of the pro-inflammatory cytokine IL-β and activates microglia. While in the stressed environment, fluoxetine decreases hippocampal inflammatory cytokines IL-β and IL-γ and downregulates microglia activity. The anti-inflammatory properties SSRI's during stress have been shown by other studies (Cheng et al., 2016; Wilson et al., 2014). However, to associate effective fluoxetine treatment with inflammation in the hippocampus is somewhat at odds with the field. Authors postulate effective neuroplastic change requires some degree of inflammatory signalling to occur, though replication of these findings by other groups is required to prove this hypothesis. As SSRI's may share convergent pathways with other classes of agents, these data highlighting the influence of the environment on neuroprotective versus neurotoxic outcomes should be considered in future work.

2. Other pharmaceutical agents

2.1 Minocycline

Minocycline is a tetracycline antibiotic with psychotropic effects being applied to a range of neuropsychiatric conditions. Used as an adjunct to standard therapies, minocycline improved negative symptoms in early schizophrenia (n=46) (Chaudhry et al., 2012). Extrapolating this to include measures of neuroprotection, Chaves et al. (2015) led a small double-blind randomised placebo-controlled trial of

add-on minocycline for early stage schizophrenia. Minocycline patients (n=16) exhibited improved symptom control, preserved grey matter volume and increased cerebral perfusion at twelve months. MRI data showed preserved grey matter in midposterior cingulate cortex and in the precentral gyrus compared to placebo. Additionally, single photon emission computed tomography displayed increased uptake of contrast in frontotemporal regions; indicative of enhanced cerebral perfusion. These are promising results despite the small size of the study.

In depression, a double blind randomised clinical placebo-controlled trial (n=71) found adjuvant minocycline led to improved clinical global impression, quality of life and social and occupational function (Dean et al., 2017). However, no significant difference in the Montgomery–Asberg Depression Rating Scale was observed between the two groups. A smaller double blind randomised clinical placebo-controlled trail of adjuvant minocycline in depression (n=41) found clinical improvement as per Hamilton Depression Rating Scale in addition to other measures (Husain et al., 2017). Lastly, a 6-week open label study of adjuvant minocycline in combination with SSRI's to treat psychotic depression (n=25) demonstrated minocycline's safety in this setting (Miyaoka et al., 2012). However, lack of control group and open-label design limit interpretation of this particular work.

As the clinical benefits of minocycline continue to be realised, understanding of its mechanism deepens also. Minocycline may be a selective Cytochrome P450 (CYP) inhibitor altering the pharmacokinetics of antipsychotics such as clozapine to raise their circulating levels and enhancing overall effect (Wehring et al., 2017). Nevertheless, minocycline appears to have direct actions of its own.

In maternal immune challenged to mice, Mattei et al. (2014) reported elevated microglial IL-β and TNFα in the hippocampus, indicative of chronic microglial activation. Furthermore, the pro-proliferative TNFα

Receptor Type 2 (TNFR2) was downregulated in hippocampal neural progenitor cells. Minocycline treatment attenuated these changes (**Table 2: Other Pharmaceutical Agents**). In a follow-up study, Mattei et al. (2017) applied RNA-sequencing to hippocampal microglia isolated from these mice. This showed a significantly altered transcriptome, which was almost entirely normalised by minocycline. This suggests minocycline could be inhibiting activated microglia, a finding that has been replicated in multiple other pre-clinical studies (Kreisel et al., 2014; Tanra, 2013; Zhu et al., 2014).

It is unclear exactly how minocycline inhibits microglial activity. It may occur by reducing oxidative stress and inflammatory cytokines which is perpetuated by aberrant microglial hyperactivity. Minocycline normalises glutathione levels and thiobarbituric acid reactive substances (TBARS) in disease models (markers of oxidative stress and lipid peroxidation respectively) (Monte et al., 2013; G. Z. Reus et al., 2015). In a mouse model of post-traumatic stress disorder, minocycline attenuate a rise in IL-1, IL-6 and TNFα in the hippocampus and frontal cortex (Levkovitz, Fenchel, Kaplan, Zohar, & Cohen, 2015).

2.2 Statins

Like minocycline, statins continue to be explored in various clinical settings as adjunct therapies. Meta-analysis suggests add-on statin therapy improves depressive symptoms with good tolerability (Salagre, Fernandes, Dodd, Brownstein, & Berk, 2016); however, larger prospective trials are required to confirm this. In patients after an acute coronary event, statins were comparable to escitalopram in reduction of depression, with the combination numerically superior to monotherapy with either (S. W. Kim et al., 2015). Simvastatin was shown to be more effective than atorvastatin at reducing depressive symptoms following coronary artery bypass grafting (GABG) surgery in a small cohort of patients (n=46) (Abbasi et al., 2015). Neither pravastatin nor lovastatin add-on therapies were shown to lessen symptom severity

in schizophrenia, though pravastatin reduced peripheral inflammatory markers (Ghanizadeh, Rezaee, Dehbozorgi, Berk, & Akhondzadeh, 2014; Vincenzi et al., 2014).

Co-administration of rosuvastatin with paroxetine and citalopram influences glutathione homeostasis and may enhance capacity for coping with oxidative stress in rats (Herbet, Izdebska, Pi tkowska-Chmiel, Poleszak, & Jagiełło-Wójtowicz, 2016). Simvastatin was used to reverse the loss of pyramidal neurons in the hippocampus of high fat diet fed mice (Can, Ulupinar, Ozkay, Yegin, & Ozturk, 2012). This morphological benefit was accompanied by alleviation of depression-like symptoms. Simvastatin shows comparable antidepressant effect to imipramine in a chronic mild stress model of depression in rats (Lin, Chang, & Lin, 2014). The antidepressant effects of statins may involve intracellular pro-survival signalling through the phosphoinositide 3 kinase (PI3K)/protein kinase B (Akt)/glycogen synthase kinase 3 beta (GSK-3β)/mechanistic target of rapamycin (mTOR) cascade. This pathway, an indicator of anabolic states, is upregulated in hippocampal neurones following an antidepressant dose of atorvastatin in mice (Ludka et al., 2016). This could be driven, at least partly, by increased mature BDNF in this brain region (Ludka et al., 2017).

2.3 Aspirin

As an irreversible inhibitor of COX1 and COX2 signalling, aspirin stimulates endogenous anti-inflammatory signals leading to reduced levels of inflammatory biomarkers and less oxidative stress (Berk et al., 2013). Aspirin does not cross the blood brain barrier but theoretically should exert neuroprotective effects through reducing overall inflammation. For example, aspirin decreases peripheral IL-6 and TNFα while also exerting antidepressant effects; a result comparable to fluoxetine and

imipramine (Guan, Shao, Xie, Chen, & Wang, 2014). These peripheral anti-inflammatory actions correlate with a central reduction in inflammatory cytokines (Li et al., 2017). This may in turn suppress microglia and protect white matter from degeneration. Co-treatment with Aspirin and DHA suppressed activation of microglia *in vitro* and increased the microglial concentration of glutathione; therefore, increasing the anti-oxidant capacity of microglia cells (Pettit, Varsanyi, Tadros, & Vassiliou, 2013). Two studies using a combination of an *in vivo* model of white matter lesions and *in vitro* oligodendrocyte precursor cells demonstrated aspirin can protect white matter from insult (Chen et al., 2014; Huang et al., 2016). Aspirin appears to promote oligodendrocyte differentiation to repair white matter lesions possibly via inhibition of Wnt/β-Catenin signalling, a regulator of cell fate.

→ Table 2: Other Pharmaceutical Agents

2.4 Cyclooxygenase-2 Inhibitors

The serum expression of COX-2 is elevated in depression (Galecki et al., 2012). A 2014 meta-analysis suggests celecoxib, a selective COX-2 inhibitor, is effective add-on therapy in depression (Kohler et al., 2014). In the years since, celecoxib has shown promise as adjunctive therapy in young manic patients (Arabzadeh et al., 2015; Mousavi et al., 2017). Adjunctive celecoxib may also improve symptoms in schizophrenia according to a recent meta-analysis (W. Zheng et al., 2017).

Highlighting the role of COX-2 inhibition in neuroprotection, Luo, Kuang, Li, Ran, and Yang (2017) inhibited COX-2 signalling via two methods in chronically stressed rats: 1) meloxicam, a COX-2 selective non-steroidal anti-inflammatory and 2) via RNA-interference. COX-2 inhibition reversed the

pro-inflammatory and anti-neurotrophic changes induced by chronic stress. This included reducing hippocampal prostaglandins and increasing hippocampal signalling through cyclic adenosine monophosphate (cAMP), protein kinase A (PKA), cAMP response binding element (CREB) and BDNF. Another study showed COX-2 inhibition with celecoxib reduces hippocampal concentrations of inflammatory markers TNFα and nuclear factor-B (NF-κB), as well as, the apoptotic marker caspase-3 in mice (Elnahas, Abou Zeid, Kawy, Hendawy, & Baher, 2016).

Collectively these human and animal data imply COX-2 inhibition may play a role in targeting neuropsychiatric symptoms with the added benefit of protecting brain structures from inflammatory insult.

2.5 Ketamine

It is suggested that altered glutamatergic signalling is a component of the pathophysiology of schizophrenia (Howes, McCutcheon, & Stone, 2015). Ketamine, a selective NMDA antagonist, is therefore used as a pre-clinical model of the disease (Monte et al., 2013). High-dose ketamine, such as is used for anaesthesia, is possibly neurotoxic to the developing brain (X. Zheng, Zhou, & Xia, 2015). Furthermore, chronic ketamine abuse is associated with an irreversible decline in brain function (Morgan et al., 2014). However, low-dose acutely administered ketamine is an emerging therapy in treatment resistant depression and suicidality (C. Kraus et al., 2017). These effects have led to interest in ketamine as a possible neuroprotective agent.

In rat models of depression, low-dose ketamine acutely influences anti-inflammatory pathways thought to be neuroprotective. Ketamine reduces hippocampal and serum levels of pro-inflammatory cytokines

IL1β, IL6 and TNFα while concurrently reducing depressive symptoms (N. Wang et al., 2015; Xie et al., 2017). This culminates in an overall reduction in ROS (Demirdas, Naziroglu, & Ovey, 2017). Additionally, ketamine influences neurotrophic pathways in the acute phase. Ketamine increases hippocampal levels of BDNF, likely via activation of adenosine monophosphate activated protein kinase (AMPK), to alleviate depression in rats (Xu et al., 2013). This rise in BDNF has been linked to maintenance of normal neuron morphology in the hippocampus of chronically stressed rats (W. X. Liu et al., 2016). Inhibition of mTOR, an intracellular mediator of BDNF and driver of synaptogenesis, significantly reduces ketamine's antidepressant effect (G. Z. Reus et al., 2016). In another pathway, ketamine increased the hippocampal level of the novel neurotrophic transcription factor activity-dependent neuroprotective protein (ADNP). This occurred simultaneously with decreased apoptosis marker, caspase-3 (B. P. Brown et al., 2015).

Collectively these data indicate a shift towards neurogenesis acutely following low-dose ketamine treatment but data on chronic outcomes is lacking. Until the lasting effects of low-dose ketamine have been properly assessed, ketamine's neuroprotective potential remains largely theoretical.

2.6 Alpha 2 Delta (α2δ) Ligands

The α2δ ligands pregabalin and gabapentin are used as treatments for neuropathic pain and have recently become known for their abuse potential (Chiappini & Schifano, 2016; Peckham, Fairman, & Sclar, 2017). Regarding neuroprotection their efficacy remains largely unknown but a small body of pre-clinical evidence indicates activation of neurogenesis as one possible avenue. Valente et al. (2012) demonstrated the neurogenic capacity of the α2δ ligands with both pregabalin and gabapentin driving the maturation of

hippocampal neuron progenitor cells *in vitro*. Interaction with α2δ subunit 2 voltage gated calcium channels and upregulation of NF-κβ signalling was suggested as a possible mechanism; NF-κβ signalling is a downstream regulator of neuron differentiation. They went on to show that pregabalin therapy ameliorated the depressed phenotype of chronically restrained mice with associated hippocampal neurogenesis *in vivo* (Valente et al., 2012). Gabapentin's positive effect on neuron differentiation has been replicated in cortical stem cells harvested from rats (Paknejad, Kebriaeezadeh, Ghahremani, Gharghabi, & Ostad, 2015). Moreover, chronic administration of gabapentin prevents behavioural abnormalities correlated with social isolation rearing in mice via an unknown mechanism (Amiri et al., 2017). Cross-sectional analysis of people receiving α2δ ligands with neuroprotective end-points would be an expedited way of assessing their potential.

3. Nutritional agents

3.1 Melatonin

Aberrant melatonin levels in the serum and cerebrospinal fluid have been observed in mood disorder patients (Bumb et al., 2016). In severe depression, serum melatonin levels are decreased in proportion to serum BDNF and are significantly lower than healthy controls (Ogłodek, Just, Szromek, & Araszkiewicz, 2016). Adjunctive melatonin has already been shown to improve the metabolic side-effects of antipsychotics (Modabbernia et al., 2014; Romo-Nava et al., 2014).

In the setting of chronic ketamine administration in mice, melatonin increases hippocampal BDNF leading to phosphorylation of Akt and extracellular signal regulated kinases 1 and 2 (ERK1/2) (pro-

survival pathways) (**Table 3: Nutritional, Hormonal and Other Agents**) (Choudhury, Singh, Palit, Shukla, & Ganguly, 2016). These actions were found to be melatonin receptor 1 and 2 (MT_1/MT_2) dependent through blockade with luzindole, an MT_1/MT_2 receptor antagonist. However, a study on hippocampal slice cultures found melatonin induced dendritogenisis through Ca^{2+} calmodulin-dependent protein kinase II (CaMKII) activation independent of MT_1/MT_2; indicating melatonin may influence neuronal structures through other mechanisms (Dominguez-Alonso, Valdes-Tovar, Solis-Chagoyan, & Benitez-King, 2015). Melatonin has demonstrated capacity to preserve hippocampal monoamine handling in disease states, in particular noradrenaline, though whether this is neuroprotective is unclear (Stefanovic et al., 2016). Finally, melatonin may also influence redox equilibrium. Either through the oxygen free radical scavenging properties of its metabolites, or, regulation of antioxidant gene transcription as was seen in a rat model of mania (Galano, Tan, & Reiter, 2013; Souza et al., 2014).

3.2 Oestrogen

The sex hormone oestrogen has a developing evidence base for neuroprotection. Using bone mineral density as a marker of cumulative oestrogen exposure, a study of female psychosis patients (n=14) found a positive correlation between oestrogen exposure and cortical thickness (van der Leeuw et al., 2013). A meta-analysis showed delayed age of menopause and longer reproductive period, also representative of cumulative oestrogen exposure, lowers risk of developing depression (Georgakis et al., 2016). Demonstrating that exogenous oestrogen can also be beneficial, ovariectomized rats were treated with escitalopram and adjunctive oestrogen. Depression-like symptoms and hippocampal architecture were both improved compared to escitalopram alone (Ibrahim, Safar, Khattab, & Agha, 2016). Mouse derived cortical cell cultures suggest oestrogen's neuroprotective effects are dependent on G-protein couple receptor 30 (GPR30) and ERK1/2 signalling (S. B. Liu et al., 2012).

3.3 Curcumin

There is preliminary evidence supporting curcumin as a therapy for depression; however, pre-clinical data implies neuroprotective potential (Lopresti, Maes, Maker, Hood, & Drummond, 2014). Curcumin has demonstrated efficacy in ameliorating depressive-like symptoms and cognitive deficit in mice submitted to CUMS. Additionally, curcumin pre-treatment raises hippocampal BDNF with upregulation of the pro-survival ERK pathway (D. X. Liu et al., 2014; L. Zhang et al., 2014). Curcumin drives production of DHA in rats leading to increased levels in the brain; therefore, presenting another potential avenue of neuroprotection (Wu et al., 2015). To date, curcumin's poor bioavailability has proven a limitation to human applications; however, ongoing efforts such as nanoformulation are working to address this (Naksuriya, Okonogi, Schiffelers, & Hennink, 2014).

→ Table 3: Nutritional, Hormonal and Other Agents

3.4 Erythropoietin

Erythropoietin (EPO) can be used as an adjunctive treatment in neuropsychiatric disease. In bipolar disorder (n=43) and major depression (n=36), add-on EPO leads to improved objective cognition, which lasts six weeks post cessation of EPO (Ott, Vinberg, Kessing, & Miskowiak, 2016). Systematic review of the literature suggests schizophrenia may also benefit from EPO induced cognitive enhancement (Fountoulakis et al., 2017). In a study of socially defeated mice, a bullying induced model of depression, EPO therapy correlated with symptom improvement as indicated by forced swim testing (Osborn et al., 2013). This was accompanied by maintained hippocampal neurogenesis. In the same study, rapamycin

administration, an mTOR inhibitor, ameliorated EPO's effect on depressive-like symptoms. However, neurogenesis was not assessed in the presence of rapamycin, so it is unclear from this study if mTOR plays a role here. Three-week administration of EPO to young mice led to an increase in hippocampal volume and an approximate 20% higher number of pyramidal neurons in CA1/CA3 hippocampal subregions (Hassouna et al., 2016). This occurred without an increase in BrdU positive cells and therefore irrespective of proliferation and raising the question of the origins of the additional pyramidal neurons. The same study used cultured neutrospheres to show that EPO decreased Sox9 and increased miR124, a transcription factor and non-coding RNA associated with neural differentiation. Thus, indicating EPO may induce differentiation of neural progenitor cells *in vivo*.

3.5 N-acetylcysteine

A systematic review of clinical trials involving NAC support its potential role in managing various psychiatric conditions including but not limited to depression, bipolar disorder and schizophrenia (Deepmala et al., 2015). Further analysis of the literature suggests NAC could have a positive impact on human cognition, though further research is required (Skvarc et al., 2017). A preliminary study of patients with psychosis (n=58) found an association between NAC treatment and improved working memory after 24-weeks (Rapado-Castro et al., 2017).

NAC is a glutathione precursor and potent antioxidant; as demonstrated by reversal of a glutathione deficient mouse model of schizophrenia (Duarte et al., 2012). When given to pregnant rats submitted to an endotoxin immune challenge, the antioxidant properties of NAC prevented permanent disorganisation of the CA3 hippocampal subregion in offspring (Rideau Batista Novais et al., 2013). By increasing glutathione and influencing the antioxidant capacity of cells, NAC may augment mitochondrial

respiratory capacity as a means of protecting against disease. NAC improves mitochondrial function in a transgenic mouse model of Huntington's disease (Wright et al., 2015).

NAC may also exert neuroprotection via glutathione independent mechanisms. Cell culture experiments suggest NAC improves heat-shock protein (Hsp) 70 chaperone function in neurones and astrocytes; therefore, protecting cells against proteotoxicity (Gleixner et al., 2017; Jiang et al., 2013). Whether this occurs *in vivo* in neuropsychiatric conditions is unknown. Current NAC formulations have limited bioavailability and short half-life, however, novel nanoparticle prodrug variations of NAC present a potential solution to this issue, nonetheless will require further assessment for indication *in vivo* (Markoutsa & Xu, 2017).

3.6 Leptin

Leptin is an adipokine produced by white adipose tissue with an emerging evidence base in neuropsychiatric disease. A meta-analysis of leptin in bipolar disorder found no association between serum leptin and the mood status (depression, mania or euthymia) of patients (Fernandes et al., 2016). More recently, an eight-year longitudinal study of bipolar patients (n=53) found low leptin and low adiponectin to be predictive of depressive relapse in the next twelve-months (Bond et al., 2017).

Adeno-associated viral vector mediated deletion of the hippocampal leptin receptor induces a depression-like phenotype in adult mice (Guo, Huang, Garza, Chua, & Lu, 2013). Conversely, leptin therapy promotes hippocampal neurogenesis and prevents the depressive phenotype associated with CUMS in rats (Garza, Guo, Zhang, & Lu, 2012).

Leptin levels in schizophrenia patients increase as BMI also increases, possibly representative of leptin-resistance secondary to antipsychotic use (Neelamekam, Nurjono, & Lee, 2014). Data is scarce relating leptin treatment to neuroprotection.

Further studies assessing the direct effect of leptin treatment or the reversal of leptin resistance, on disease related brain structures are required.

3.7 Omega-3 polyunsaturated fatty acids

Dietary omega-3 polyunsaturated fatty acids (PUFAs) may reduce oxidative stress and prevent the onset of mood symptoms. A longitudinal study of middle aged Puerto Ricans (n=787) showed that in people with a high burden of oxidative stress, depressive symptoms were more common when their omega-3 index was low (Bigornia et al., 2016).

Omega-3 index is the combined total of serum eicosapentaenoic acid (EPA) and DHA as looking at omega-3 in isolation is unlikely to reveal the entire story. Recently, more attention has been paid to the ratio of omega-6 to omega-3 PUFAs in relation to psychiatric disease. The baseline ratio of omega-6 fatty acids to omega-3 fatty acids has a positive correlation with the risk for development of mood disorders in high risk young adults (n=69) (Berger et al., 2017). A similar observation was made in young adults at ultra-high risk of psychosis (n=95) (Pawelczyk, Trafalska, Kotlicka-Antczak, & Pawelczyk, 2016).

In light of such evidence, omega-3 PUFA supplementation continues to be tested as augmentation therapy in neuropsychiatric disease with mixed results. In hepatitis C patients receiving interferon alpha (INFα) therapy, depression is a common adverse effect (Machado et al., 2017). EPA but not DHA

supplementation reduced the percentage of patients (n=154) developing depression while on INFα therapy (Su et al., 2014). A randomized trial of older adults at risk of depression (n=51) found omega-3 PUFA supplementation was associated with reduced thalamic oxidative stress and attenuation of symptoms (Duffy et al., 2015). In young psychotic patients, or those at ultra-high risk of psychosis, omega-3 PUFA supplementation increased total antioxidant capacity and reduced symptom severity (Pawelczyk, Grancow-Grabka, Trafalska, Szemraj, & Pawelczyk, 2017; Smesny et al., 2015).

However, multiple other studies have found omega-3 PUFAs to have no, or even negative effects on mental state. A multicentre randomised double-blind clinical placebo control trial showed omega-3 PUFAs plus cognitive behavioural case management in ultra-high risk of psychosis patients (n=301) did not slow conversion to psychosis over a 6-month period (McGorry et al., 2017). In a study of patients at high risk of post-traumatic stress disorder, omega-3 PUFAs had no effect serum BDNF or mental state (Matsuoka et al., 2015). Finally, a randomised double-blind clinical placebo control trial of add on EPA and/or Vitamins C + E in acute schizophrenia (n=99) found these agents to worsen psychosis (Bentsen, Osnes, Refsum, Solberg, & Bohmer, 2013). To explain these discrepancies, groups have postulated omega-3 PUFAs could have opposing neuroprotective or neurotoxic effects depending upon disease stage, for example, prodromal phase versus acute exacerbation of schizophrenia.

3.8 Ebselen

Ebselen is an organoselenium based molecule that mimics the actions of lithium and glutathione peroxidase (endogenous antioxidant), making this currently unmarketed pharmaceutical an attractive

prospect in neuroprotection. Ebselen has been shown in mice to cross the blood brain barrier to inhibit inositol monophosphatase (IMPase), a putative target in bipolar disorder, and exert lithium like effects in animal models of mania (Singh et al., 2013). The same group have shown ebselen to inhibit IMPase in the anterior cingulate cortex of healthy human subjects with significant effects on emotional processing (Singh et al., 2016); findings that have been subsequently replicated (Masaki, Sharpley, Cooper, et al., 2016; Masaki, Sharpley, Godlewska, et al., 2016). Early life treatment with ebselen is comparable to NAC in the prevention of schizophrenia-like symptoms in rats subjected to neonatal hippocampal lesions (Cabungcal et al., 2014). *In vitro* analysis of rat astrocytes indicate ebselen may cause endoplasmic reticulum stress and neurotoxicity, casting some doubt over its neuroprotective potential (Santofimia-Castano et al., 2016). However, eblesen's supposed mechanisms *in vivo* and promising clinical data warrant further investigation as a neuroprotective option.

Conclusion

The evidence presented here is a testament to the significant progress made in neuroprotection. Lithium's maintenance of neurostructural integrity in bipolar disorder is the most pertinent example. However, lithium's story also highlights the limitations in current assessment tools and understanding. MRI results consistent with neuroprotection do not necessarily correlate with functional attenuation of neuroprogression – reduced vulnerability to relapse, increased responsiveness to treatment and delayed cognitive/functional decline. Agents such as aripiprazole or EPO may demonstrate functional improvement in cognition but have little evidence regarding neurostructural benefit. A deeper mechanistic understanding of the agents presented here may explain these discrepancies in future. At this stage, it is also unclear if neuroprotective benefit accrues by directly reversing the operative pathways or via augmentation of state related activation of such pathways, as seem to be the case with antidepressants. Future work may show that agents from multiple classes induce undirected susceptibility to change rather than driving neuroprotective alterations irrespective of environmental factors. Finally, it may be that neuroprotection may require not a single agent but rather multiple adjunctive therapies acting in synchrony to achieve an effect. For example, the use of melatonin or other agents to augment the metabolic side effects of second-generation antipsychotics to improve adherence and maximise benefit. In any case, further validation is ultimately required at this time.

The studies reviewed here were heterogeneous in almost every respect, ranging from clinical trials to cell culture experiments with only some studies having neuroprotection as a primary outcome measure. Furthermore, the scope of this review was limited to neuropsychiatric disorders with reference to neuroprotection in other conditions such as neurodegenerative, cerebrovascular and traumatic brain injuries only where directly relevant to discussion. In order for neuroprotection to be assessed with

confidence, prospective analysis with neuroprotection as the primary outcome and multi-modal analysis including assessment of neurostructural benefit, symptomatic/cognitive effect and biologic/genetic markers of mechanism are required.

Conflicts of Interest

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Patents:

Michael Berk is a co-inventor of two provisional patents regarding the use of NAC and related compounds for psychiatric indications, which, while assigned to the Mental Health Research Institute, could lead to personal remuneration upon a commercialisation event.

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	Neurostructural Integrity		Neurogenic Balance		Inflammatory State		Oxidative and Nitrosative Stress	
	Protects cortical volume	*Improves white matter*	*Central*	*Peripheral*	*Central*	*Peripheral*	*Central*	*Peripheral*
Lithium	Yes	Yes	Rat brain: ↑BDNF, ↓Apoptosis		Rat brain: ↓TLR4, ↓NFκB		↓Oxidative stress	
Clozapine			Mouse brain: ↑BDNF, ↑Proliferation			Rat: ↓toxic TRYCATs, ↓COX signalling	Rat brain: ↑DHA signalling	
Aripiprazole				↑BDNF				
Olanzapine			Rat brain: ↑BDNF, ↓Apoptosis			Rat: ↑TNFα, ↑ IL1β, ↑ IL6		
Risperidone			Rat brain: ↑BDNF, ↓Apoptosis					↓Oxidative stress
Paliperidone					Mouse brain: ↑NRF2, ↓Microglial activity		Rat brain: ↓Oxidative stress	
Quetiapine		Mouse brain: Yes			Mouse brain: ↓Microglial activity		Mouse: ↑mitochondrial activity	
Antidepressants			Mouse brain: ↑BDNF, ↑Hippocampal proliferation	↑BDNF	Rat brain: ↓ IL-β, ↓TNFα	↓IL-4, ↓IL-6, ↓IL-10, ↓ IL-β, ↓toxic TRYCATs	Rat brain: ↑mitochondrial activity	

Table 1: Psychotropic Agents. Evidence of neuroprotective effects and suggested mechanisms of action for psychotropic agents presented in review. Data is divided by mode of detection, either centrally from brain tissue or peripherally from serum. All data represents human clinical studies unless explicitly stated in table. **Key:** ↑ = Increased ↓ = Decreased. For other abbreviations, refer to **Abbreviations.**

	Neurostructural Integrity		Neurogenic Balance		Inflammatory State		Oxidative and Nitrosative Stress	
	Protects cortical volume	*Improves white matter*	*Central*	*Peripheral*	*Central*	*Peripheral*	*Central*	*Peripheral*
Minocycline	Yes				Mouse brain:↓ IL-β, ↓IL-1, ↓IL-6, ↓TNFα, ↓Microglial activity			
Statins			Rat brain: ↑mTOR					Rat: ↑glutathione
Aspirin		Rat brain: Yes				↓IL-6, ↓TNFα		
Cyclooxygenase 2 Inhibitors			Rat brain: ↑BDNF, ↓apoptosis		Rat brain: ↓TNFα, ↓ NF-κB			
Ketamine			Rat brain: ↑BDNF, ↑ADNP, ↓apoptosis		Rat brain: ↓ IL1-β, ↓IL-6, ↓TNFα			
Pregabalin			Mouse brain: ↑hippocampal neurogenesis					

Table 2: Other Pharmaceutical Agents. Evidence of neuroprotective effects and suggested mechanisms of action for pharmaceutical agents presented in review. Data is divided by mode of detection, either centrally from brain tissue or peripherally from blood. All data represents human clinical studies unless explicitly stated in table. **Key:** ↑ = Increased ↓ = Decreased. For other abbreviations, refer to **Abbreviations.**

	Neurostructural Integrity		Neurogenic Balance		Inflammatory State		Oxidative and Nitrosative Stress	
	Protects cortical volume	*Improves white matter*	*Central*	*Peripheral*	*Central*	*Peripheral*	*Central*	*Peripheral*
Melatonin			Mouse brain: ↑BDNF, ↑ERK1/2					Rat: ↓Oxidative stress
Oestrogen	Yes		Rat brain: ↑Hippocampal architecture Cortical cells: ↑ERK1/2					
Curcumin			Mouse brain: ↑BDNF, ↑ERK1/2				Rat brain: ↑DHA signaling	
Erythropoietin	Mouse brain: Yes		Mouse brain: ↑proliferation					
N-Acetylcysteine							Mouse brain: ↓Oxidative stress	Mouse:↓Oxidative stress
Leptin			Rat brain: ↑hippocampal neurogenesis					
Omega-3 Fatty Acids							↓Oxidative stress	↑Antioxidant capacity
Ebselen			Mouse brain: ↓IMPase					

Table 2: Nutritional, Hormonal and Other Agents. Evidence of neuroprotective effects and suggested mechanisms of action for nutritional, homonal and other agents presented in review. Data is divided by mode of detection, either centrally from brain tissue or peripherally from blood. All data represents human clinical studies unless explicitly stated in table. **Key:** ↑ = Increased ↓ = Decreased. For other abbreviations, refer to **Abbreviations.**