Novel and emerging treatments for major depression

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Depression is common, costly, debilitating, and associated with increased risk of suicide. It is one of the leading global public health problems. Although existing available pharmacological treatments can be effective, their onset of action can take up to 6 weeks, side-effects are common, and recovery can require treatment with multiple different agents. Although psychosocial interventions might also be recommended, more effective treatments than those currently available are needed for people with moderate or severe depression. In the past 10 years, treatment trials have developed and tested many new targeted interventions. In this Review, we assess novel and emerging biological treatments for major depressive disorder, evaluate their putative brain and body mechanisms, and highlight how close each might be to clinical use.

Lancet 2023; 401: 141–53

Published Online December 16, 2022 https://doi.org/10.1016/S0140-6736(22)02080-3

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Introduction

Depression is a major global mental health challenge and the leading cause of mental-health-related disability worldwide.[1] It is common and frequently recurrent, with a global prevalence of 4·4%.[2] For many people with depression, onset is in mid to late adolescence (eg, age 14 to 25 years); median 12-month prevalence in this age group is 4–5%.[3] Major depressive disorder (MDD) negatively affects education, relationships, and employment and is prospectively associated with obesity, cardiac disease, and early death, including suicide.[4–6] The financial costs are substantial and closely linked to working days lost, reduced productivity, and absenteeism. The functional effects of depression can be particularly severe in adults older than 18 years, in whom comorbidity with physical health problems has further effects and leads to complexity in treatment options.

Current biomedical models of depression conceptualise it as a disorder of neural networks incorporating changes in widely distributed brain areas,[7] with effective antidepressants improving synaptic plasticity[8] and acting as modulators of monoamines (eg, serotonin, noradrenaline, and dopamine). Although guidelines, such as those from the National Insitute for Health and Care Excellence in the UK,[9] recommend a comprehensive biopsychosocial approach to treating depression and evidence suggests psychological interventions, social support, and exercise are important, treatment with medication is often essential in moderate or severe depression. Although antidepressants are effective, a third to half of people with MDD do not respond to multiple antidepressants,[10,11] and more might only obtain a partial response. People with depression who do not respond to two trials of antidepressants are often categorised as having treatment-resistant depression (TRD). Typically, individuals have to wait at least 4 weeks before a potential response to current antidepressants occurs and side-effects, such as sexual dysfunction, loss of libido, headache, gastrointestinal symptoms, anxiety, and agitation, are common.

Therefore, there is a need to develop, test, and understand the effectiveness of new agents or treatment modalities, ideally with a more rapid onset of action, better tolerability, and with the potential for greater effectiveness than existing antidepressants in people for whom current antidepressants have failed. In this Review, we aim to provide an evaluation of novel biological treatments using a systematic approach to highlight the best evidence currently available, with a particular emphasis on mechanism of effect, and provide an outline through which new treatments might be clinically useful. Although not a formal systematic review, we outline search terms and strategy.

N-methyl-D-aspartate modulators

Glutamate functioning is known to be disturbed in areas of the brain that are associated with depression.[12] It is the most common brain excitatory neurotransmitter, and levels of glutamate are increased by chronic stress. This glutamatergic upsurge can decrease synapse connectivity and result in deficits in γ-aminobutyric acid (GABA) functioning, the most abundant inhibitory brain

Search strategy and selection criteria

We searched the Cochrane Central Register of Controlled Trials, PubMed, Embase, and PsycINFO for literature published between Jan 1, 2015, and Nov 17, 2021, that focused on depression and novel treatments. We also searched for unpublished and ongoing studies in ClinicalTrials.gov. All included papers had to have at least an abstract published in English. The search terms used were "depress*" OR "dysthymi*" OR "mood disorder" OR "affective disorder". These terms were then combined with multiple groups of novel treatment search terms: "psychedelic" OR "psilocybin" OR "LSD" OR "lysergic acid diethylamide" OR "ayahuasca" OR "MDMA", "Esketamine" OR "ketamine" OR "NMDA antagonist", "transcranial magnetic stimulation" OR "rTMS" OR "theta burst TMS", "transcranial direct current stimulation" OR "tDCS" OR "neurostimulation", "GABA" OR "NMDA", "inflammation" OR "neuroinflammation" OR "anti-inflammatory" OR "microbiome", "deep brain stimulation" OR "DBS", and "comorbid depression". Potentially relevant papers were identified via title and abstract searches, then full texts were obtained. We reviewed papers on the efficacy of interventions (eg, randomised controlled trials) and papers that provided mechanistic insight into novel treatments.

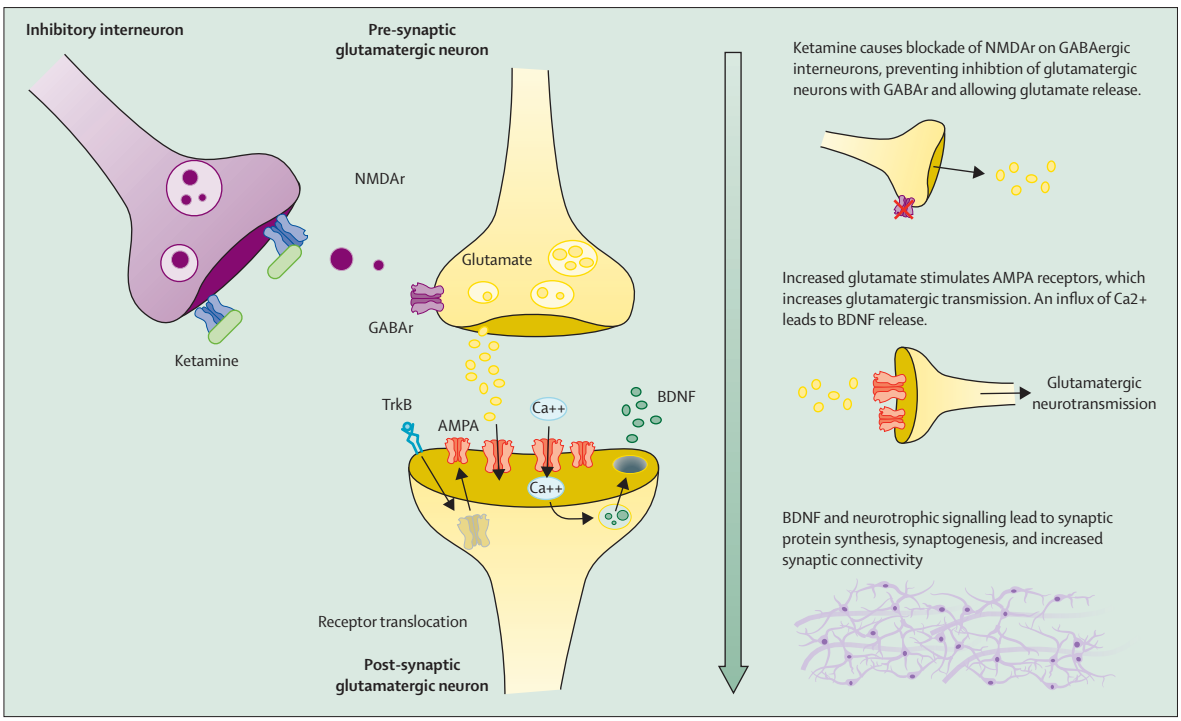

Figure 1: **Mechanism of action of ketamine**
Figure created with BioRender.com. AMPA=α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid. BDNF=brain-derived neurotrophic factor. Ca2+=calcium. Ca++=calcium. GABAr=γ-aminobutyric acid receptor. NMDAr=N-methyl-D-aspartate receptor. TrKb=tropomyosin receptor kinase B.

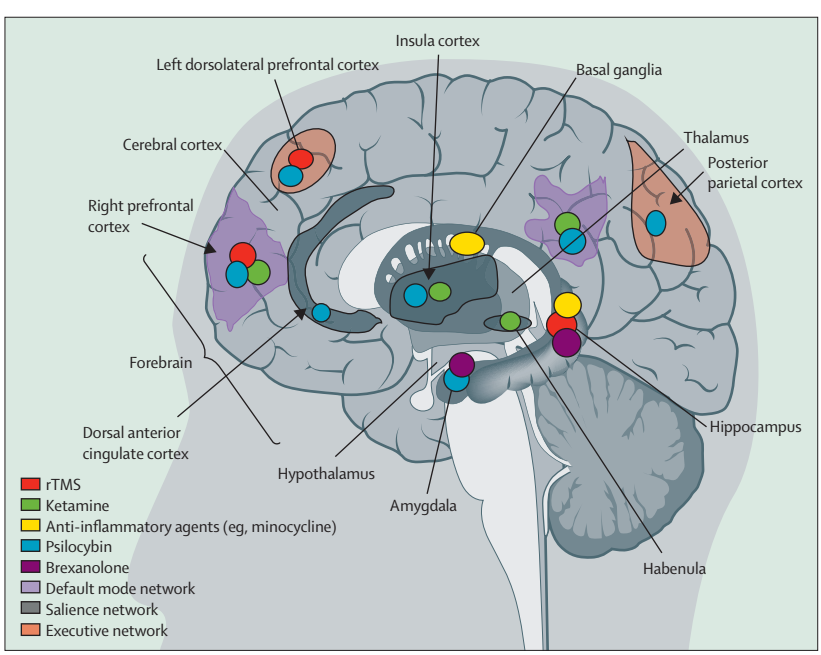

Figure 2: **Reported location of effect of novel and emerging treatments for depression**
rTMS=repetitive transcranial magnetic stimulation.

neurotransmitter. Both glutamate and GABA, or the balance between them in different areas of the brain, are thought to be one of the final common pathways in depression and the focus of antidepressant action.

Ketamine

Research on ketamine has substantially increased because of interest in its novel and rapid action. Ketamine contains two enantiomers, R-ketamine and S-ketamine. Both are glutamatergic agents acting as antagonists at the N-methyl-D-aspartate (NMDA) receptor in the brain (figure 1). Ketamine also acts to increase the conversion of brain-derived neurotrophic factor (BDNF),[13] an important agent involved in neural plasticity and known to be atypical in depression. Reported areas of brain action for ketamine and other agents have been delineated (figure 2). Ketamine in clinical use for depression can be administered intravenously, intramuscularly, in tablet form, and intranasally (esketamine is now licenced by the US Food and Drug Administration [FDA], although not yet sanctioned by the National Institute for Health and Care Excellence). Intravenous dosage is commonly 0·5 mg/kg delivered for 30–40 min with blood pressure, heart rate, and temperature monitoring, and can be administered alone or as an adjunct to another antidepressant.

Meta-analyses have assessed ketamine efficacy, with most studies focusing on its use in TRD. Ketamine infusion appears to be effective in alleviating depressive symptoms in TRD. In seven placebo-controlled randomised controlled trials (RCTs), depression scores were significantly reduced after treatment with ketamine compared with placebo, with a standardised mean difference (SMD) of 0·68 (95% CI 0·46 to 0·9) after 24 h

but with a rapid reduction of effect during the week after treatment (SMD 0·77 at 24 h *vs* 0·49 at 7 days after infusion). A systematic review of 28 primary studies from 2009 to 2019, with 19 being suitable for meta-analysis evaluating the efficacy of ketamine infusions in people with TRD, indicated efficacy in clinical response (pooled odds ratio [OR] 6·33, 95% CI 3·33 to 12·05) on the basis of data from seven placebo-controlled randomised controlled trials, although the largest response was found after 24 h. Data from four studies indicated an effect on clinical remission favouring ketamine over placebo (OR 5·11, 95% CI 2·15 to 12·17) 24 h after infusion with reductions in effectiveness after 7 days.[14] There might be some sustained antidepressant effect after treatment for up to 6 weeks,[15] although the large effect size (g –1·36, 95% CI –2·69 to –0·04, t4 –2·85, p=0·05) of the effectiveness of ketamine reported in this meta-analysis was based on only five studies in which there was a high degree of heterogeneity and Eggers test for publication bias could not be completed due to an insufficient number of studies.

A similar pattern of effect has been found for intranasal esketamine[16] in people who are non-responsive to at least two previous antidepressants when administered as an adjunct to a recognised antidepressant, albeit from evidence with a range of biases. Treatment is usually administered twice per week. One randomised, double-blind, active-controlled study (TRANSFORM-2)[17] of three short-term clinical trials for 28 days showed that esketamine improved depressive symptoms when administered with an oral antidepressant compared with placebo (least squared mean difference [LSMD] –4·0, SE 1·69, 95% CI –7·31 to –0·64, p=0·020). Although the LSMD was similar in TRANSFORM-1 (–3·2) and TRANSFORM-3 (–3·6), a statistically significant difference between esketamine and placebo was not found in these studies. One of the negative trials (TRANFORM-3,[18] a phase 3, double-blind, randomised trial) was in people aged 65 years or older. In the SUSTAIN-1 relapse prevention trial in people who had responded to esketamine, continued treatment with esketamine and an oral antidepressant increased time to relapse compared with placebo (log-rank p<0·001, number needed to treat [NNT] 4).[19] The SUSTAIN-2 open-label, long-term trial found a sustained effect for 1 year in people who respond to esketamine.[20,21] The reduction in depressive symptoms can occur within 1 day.[17] If treatment is maintained for up to 6 months, relapse can be reduced by 51% in remitted patients if they are also taking their previous antidepressant.[19,21] Phase 2 and phase 3 trials indicate that the effects of esketamine are stopped when medication is stopped,[22] which is not unlike effects that could be stopped with cessation of other antidepressants.

An overview of systematic reviews and meta-analyses[16] of the effectiveness of ketamine and esketamine published in 2022 showed that bias within individual studies had not been assessed and funding sources were not always clear. The quality of the systematic reviews and meta-analyses were also considered to be critically low[16] with the AMSTAR-2 quality assessment. Results of studies of the effectiveness of ketamine and esketamine should be considered in this context.

In a large network meta-analysis (n=8282 TRD patients, of which only 116 were allocated to NMDA medication) of augmenting agents completed in 2020, NMDA modulators were better than placebo in reducing depressive symptoms (effect size 0·91, 95% CI 0·67–1·16).[23] Minocycline, an NMDA antagonist, appeared to have a particularly large effect size. NMDA modulators had the highest chance of being an effective treatment.[23] A specific comparison with augmenting with antipsychotic agents indicated that intranasal esketamine augmentation is more effective (mean difference 4·09, 95% CI 2·01–6·17) than antipsychotic augmentation (mean difference 2·05, 95% CI 1·51–2·59) in reducing depressive symptoms.[24]

In people with TRD having electroconvulsive therapy (ECT), there is low quality evidence—established by GRADE criteria—to indicate that the combination of ketamine and propofol, a common anaesthetic, results in a rapid reduction of depressive symptoms after a single ECT session.[25] Although this signal of a treatment effect is important because of the high morbidity of people who are treated with ECT, evidence does not suggest that ketamine agents are an effective alternative to ECT when managing TRD.[26] Evidence that ketamine agents could reduce suicidality in people with MDD has contradictory findings, and doubts remain about the stability, nature, and persistence of any effect.[16]

Therapeutics is a particularly difficult issue in adolescent depression, with few agents shown to have tangible action. A single available randomised trial (n=17) of ketamine administered intravenously, with midazolam as a control, indicated an acute reduction of depressive symptoms (effect size 0·78) after 24 h in people aged 13–17 years, with these improvements maintained at day 14 of follow-up. The main adverse effect was transient dissociation.[27] Long-term studies examining the efficacy and side-effects of ketamine are urgently needed (table 1). The evidence in people older than 60 years is mixed, with one positive[28] trial of subcutaneous ketamine in people with TRD and one negative trial[18,29] of intranasal ketamine in people with TRD.

Although depressive symptom reduction is clinically important, a return of functioning is a priority for patients. RCT evidence that ketamine leads to improved functioning is scarce, with analyses not completed in two trials because there was no difference in the primary depression endpoint.[18,30] A third study, a randomised, double-blind trial, indicated an improvement in functioning 4 weeks after treatment with esketamine compared with placebo, as measured by the Sheehan Disability Scale (effect size 0·48, 95% CI 0·17–0·78), which focuses on disruption of work or school life, social life, and family responsibilities; days not attending work or school; and days that the individual was unproductive.[17]

	Major depressive disorder	Treatment-resistant depression	Administered with electroconvulsive therapy	People older than 60 years	People younger than 18 years	Post partum	Proximity to routine use
Brain stimulation	..	..	..	..	..	..	..
rTMS	Evidence exists	Evidence exists	..	Evidence exists	Evidence exists	Evidence exists	4
tDCS	Evidence exists	Evidence exists	..	..	..	..	3
Deep brain stimulation	..	Evidence exists	..	..	..	..	1
NMDA modulators	..	..	..	..	..	..	..
Intravenous ketamine	Evidence exists	Evidence exists	Evidence exists	Evidence exists	Evidence exists	..	3
Intranasal ketamine	..	Evidence exists	..	..	..	..	4
Dextromethorphan	..	Evidence exists	..	..	..	..	1
Esmethadone	..	Evidence exists	..	..	..	..	1
Anti-inflammatory agents	Evidence exists	Evidence exists	..	..	..	..	2
GABA modulators	..	..	..	..	..	..	..
Intravenous brexanolone	..	..	..	..	..	Evidence exists	4
Glucosamine	Evidence exists	..	..	..	..	..	1
Psychedelics	..	..	..	..	..	..	..
Psilocybin	..	Evidence exists	..	..	..	..	1
Ayahuasca	..	Evidence exists	..	..	..	..	1
Others	..	..	..	..	..	..	..
Pimavanserin	..	Evidence exists	..	..	..	..	2
Photobiomodulation	Evidence exists	Evidence exists	..	..	..	..	1

1=results of efficacy trials available. 2=results of effectiveness trials available. 3=used in specialist centres (eg, tertiary and regional specialist centres). 4=regulatory approvals have been acquired. GABA=γ-amino butyric acid. NMDA=N-methyl-D-aspartate. rTMS=repetitive transcranial magnetic stimulation. tDCS=transcranial direct current stimulation.

Table 1: **Potential target populations by novel treatment and proximity to routine use**

Side-effects of intravenous ketamine are typically described as mild, but include drowsiness, dizziness, poor coordination, blurred vision, and feeling strange or unreal. The most common side-effects of intranasal esketamine appear to be dissociation, headache, nausea, vertigo, altered sense of taste, and sleepiness.[16] A robust review of the side-effects of ketamine agents highlighted potential selective reporting bias in existing studies.[31] There is also concern about people misusing these agents, but the cost of prescribed ketamine could reduce the risk of diversion to the recreational-use market. A WHO expert committee did not consider the risk of dependence to be high enough to categorise ketamine for scheduling or international control.[32]

Dextromethorphan

Ketamine, and its purported mode of action, provide proof of principle that agents targeting glutamate signalling might be important in the development of new antidepressants. Dextromethorphan is known to inhibit NMDA receptors and has effects at serotonin and norepinephrine transporters;[33] it is already approved in the USA for use in pseudobulbar affect. With positive results in rodent models, clinical studies, including phase 2 trials,[34] indicated better remission rates in people with TRD at 6 weeks follow-up with combined dextromethorphan and bupropion than with bupropion alone (47% *vs* 16%). In the large, phase 3 GEMINI trial (n=327),[35,36] twice per day combination treatment of dextromethorphan and bupropion resulted in a significant reduction in Montgomery-Åsberg Depression Rating Scale scores after 1 week and up to 6 weeks compared with placebo (week 1 –7·3 *vs* –4·9, p=0·007; week 6 –16·6 *vs* –11·9, p=0·002). On Aug 19, 2022, the FDA approved the dextromethorphan plus bupropion combination for the treatment of MDD.

Esmethadone

Esmethadone is an opioid-inactive isomer of racemic methadone that binds to the NMDA receptor with low affinity and potency. The potential of esmethadone for antidepressant action could be a function of increasing plasma BDNF[37] or changing synaptic plasticity via the NMDA receptor complex. Esmethadone is reported not to have clinically meaningful opioid effects and is not considered to have potential for people to misuse it. Although the agent also has affinity for monoamine receptors, the extent of this binding makes the monoamine receptor action an unlikely primary mechanism. In a phase 2a, placebo-controlled, double-blind trial of patients with MDD who had not responded to between one and three antidepressants in the current episode of depression and who were taking a selective serotonin reuptake inhibitor, a serotonin–norepinephrine reuptake inhibitor, or bupropion, there was a significant improvement in depressive symptoms after 4 days and 7 days of taking daily oral esmethadone, which was sustained for 1 week after the last dose. The effect size was large (0·9 for 25 mg at 14 days and 1·0 for 50 mg at 14 days compared with placebo)[38] and common side-effects were headache, constipation, nausea, and somnolence.

Brain stimulation

Repetitive transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is a form of non-invasive brain stimulation that does not require an anaesthetic; the TMS machine generates a magnetic field that stimulates particular brain areas. This process can lead to changes in neuronal excitability, triggering effects between cortical and subcortical structures. Areas that are particularly relevant to TMS treatment are the left dorsolateral prefrontal cortex, which is known to be underactive in depression and linked to treatment resistance, and the right prefrontal cortex, which might be overactive in people with depression. The left dorsolateral prefrontal cortex is typically repeatedly stimulated with high-frequency, repetitive TMS (rTMS), whereas the right prefrontal cortex is typically stimulated with low-frequency TMS. rTMS usually involves 30–45-min treatment episodes once per day for at least 4 weeks. As might be expected, placebo response is large, but is lower in people with severe depression than in people with mild or moderate depression and is not associated with sex or age.[39]

A health technology assessment published in 2021 in Ontario, Canada, assessed data from nine systematic reviews and 58 primary studies reporting on the effectiveness of rTMS compared with sham treatment in adults with TRD. Although there are various TMS modalities, the authors concluded that rTMS is an effective treatment. However, they also concluded that different rTMS modalities do not differ in effectiveness.[40] The meta-analysis investigating the response rate to rTMS compared with sham treatment showed that the absolute risk reduction was approximately 23% (95% CI 15% to 32%), and NNT was 4. These results have been replicated in other reviews,[41] which also suggest that rTMS is not as effective as ECT in this patient population.

Many trials indicate no side-effect differences between sham treatment and active treatment, which would seem improbable given the tenet that if an intervention is powerful enough to be effective it is powerful enough to cause side-effects. However, headache and scalp discomfort appear to be the most reported side-effects, then fatigue, pain, dizziness, insomnia, eye and nasal issues, and gastrointestinal issues. High-quality data assessing whether rTMS leads to emergent hypomania in people with unipolar depression are not available, but current evidence indicates that it does not.[42] There is evidence that rTMS can affect affective switches in people with bipolar disorder.[43]

Researchers have investigated various ways to reduce the treatment burden of rTMS. Accelerated protocols have tested administration of rTMS more than once per day. Although the quality of the evidence is not high, it suggests that the effectiveness of 10 Hertz (Hz), high-frequency rTMS with 2–15 sessions per day is not inferior to once per day protocols,[44,45] with response rates of 36–56% in people with depression. With θ-burst stimulation (eg, 50 Hz), treatment sessions typically have a shorter duration than conventional rTMS, offering an acceptability advantage. Data from RCTs (n=294) and four uncontrolled clinical trials (n=297) suggest a pooled significant effect on response (effect size 0·38; CI: 0·29–0·48) and on remission (effect size 0·20, CI: 0·13–0·29).[46]

The effects of rTMS appear to be durable for 1 year, with meta-analyses suggesting that among people who have initially responded (ie, n=247, nine prospective or retrospective studies), 46·3% (CI 32·6–60·7) have a sustained response after 1 year. Female sex and receiving maintenance treatment were associated with increased durability.[47] Comorbid anxiety symptoms and incomplete response might be associated with relapse after rTMS.[48]

rTMS could potentially be valuable in the treatment of depression in adults older than 65 years. The prospect of a biological treatment that does not interfere with medication for physical comorbidity could be invaluable. Of seven RCTs that compared rTMS with sham treatment in adults with a mean age of more than 55 years—most with small samples—three found a significant difference, although the endpoint for most trials was 2 weeks.[49] The response rate from both RCTs and uncontrolled studies was highly variable, ranging from 6% to 54%.

In peripartum depression (ie, during the gestational period and up to 4 weeks after birth), a meta-analysis indicated a positive effect of rTMS (effect size 1·394, 95% CI 0·94–1·84) with few severe side-effects to the birthing parent or the baby.[50] This finding is particularly important as many people do not want to take medication during pregnancy because of concerns about effects on the fetus. Results show an effect in post-partum depression, but

high-quality evidence is still needed.[51] Similarly, rTMS appears to be effective in the treatment of adolescent depression, although only from open-label studies and non-controlled trials.[52] The only RCT with a sham treatment comparison in adolescent depression indicates rTMS did not differ significantly from sham treatment in this population.[53]

Transcranial direct current stimulation

Transcranial direct current stimulation (tDCS) involves applying a weak electrical current to the scalp across an anode and cathode, often by the use of a cap. Treatment usually involves five to ten stimulations per day for up to 6 weeks. The sham response is large.[54] However, a 2020 individual patient data meta-analysis incorporating nine studies and 572 participants indicated tDCS was significantly better than sham treatment in terms of response (30·9% *vs* 18·9%; NNT 9) and remission (19·9% *vs* 11·7%, NNT 13).[55] No significant differences in all-cause discontinuation between active treatment and sham treatment suggest good acceptability. tDCS is considered to be safe and well tolerated but reported side-effects in case reports do include one case of seizure in an individual with pre-existing epilepsy and skin burns under the anode and cathode in a different individual. Evidence also indicates an overall rate of 3·3% risk of emergent mania in people with unipolar depression, an increased odds of emergent mania of 5·01 (95% CI 1·37–18·26, p=0·015), and a pooled risk difference of 0·031 (0·011–0·050, p=0·002) compared with sham treatment.[56]

Deep brain stimulation

Deep brain stimulation (DBS) is a neurosurgical intervention assessed for use in severe TRD. Studies have investigated stimulation of various brain regions, including the ventral capsule, ventral striatum, nucleus accumbens, and subcallosal cingulate gyrus. Syntheses of small clinical trials, many without randomisation, suggest a potential benefit,[57] but this is independent of stimulation target. Side-effects include surgery-related (eg, swollen eye), somatic (eg, headaches), and psychiatric (eg, exacerbation of depression and agitation) side-effects. Despite evidence from systematic reviews, an RCT with a control group having sham treatment failed to find an effect of reducing depression with DBS, specifically targeting the ventral capsule and ventral striatum.[58]

γ-amino butyric acid modulators

Cognitive distortions, including in episodic memory, impaired learning, impaired attention, negative bias, and poor problem solving, are all common features of depression. Evidence has highlighted the potential of

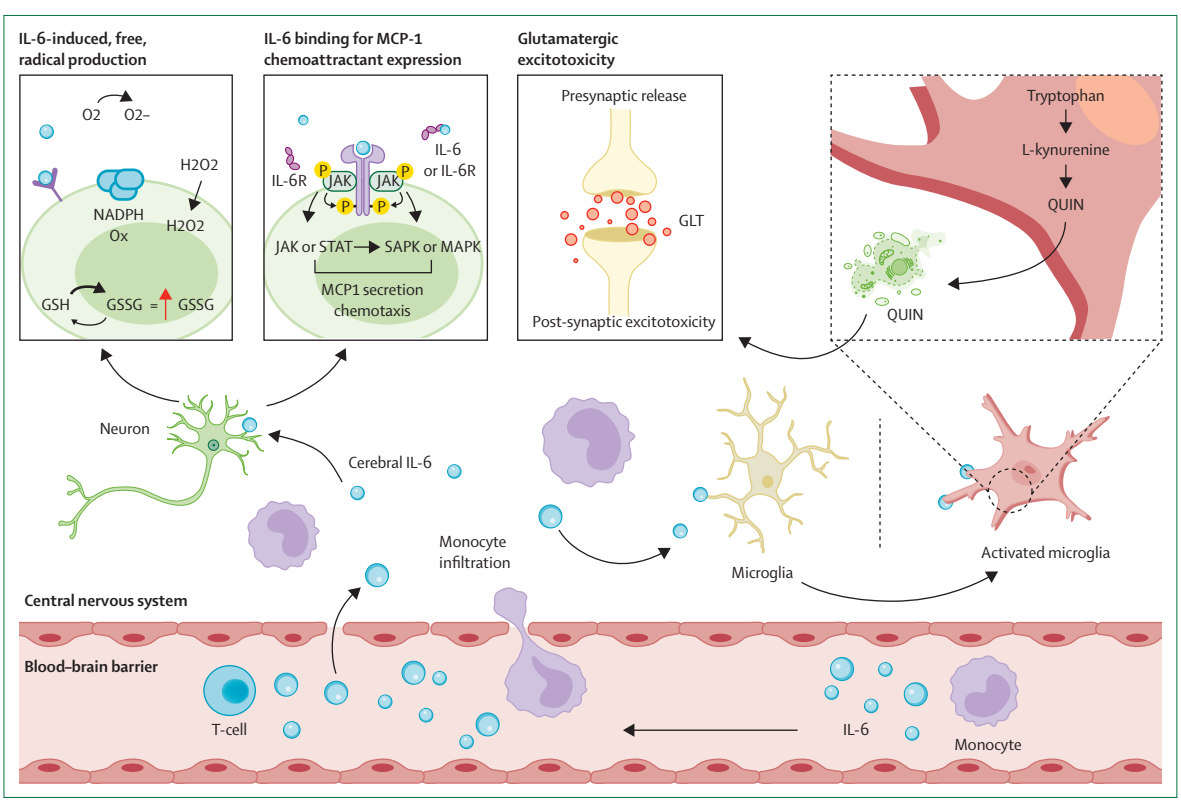

Figure 3: **Potential mechanistic targets of anti-inflammatory agents**
Figure created with BioRender.com. GLT=glutamate. GSH=glutathione. GSSG=glutathione disulfide. H2O2=hydrogen peroxide. IL-6=interleukin 6. IL-6R=interleukin 6 receptor. JAK=janus kinase. MAPK=mitogen-activated protein kinase. MCP-1=monocyte chemoattractant protein-1. NADPH=nicotinamide adenine dinucleotide phosphate. O2=oxygen. QUIN=quinolinic acid. SAPK=stress-activated protein kinase. STAT=signal transducer and activator of transcription.

GABA inhibition in these cognitive distortions.[59] In a magnetic resonance spectroscopy imaging study, reduced GABA was apparent in MDD patients with anhedonia.[60]

Brexanolone, a progesterone metabolite, is a positive modulator of the GABA receptor that exerts effects at both synaptic and extrasynaptic levels. Primarily studied in post-partum depression, double-blind RCTs have shown a brexanolone infusion led to a rapid reduction in anxiety and depression in people with post-partum depression.[61,62] Brexanolone received FDA approval in 2020 in the USA.

Glucosamine normalises GABA antagonism with additional anti-inflammatory effects. Preclinical evidence suggests it could be effective in depression as it reverses social defeat in mice models. However, a 4-week, small, open-label pilot study of glucosamine as monotherapy did not show an effect in people with depression.[63] No adverse effects were seen; definitive research is needed.

Anti-inflammatory agents

The proposal that immune dysfunction, or more specifically, non-resolving low-level inflammation, could be relevant in depression and a target for treatment was first proposed in the early 1900s, with vaccine therapy and the potential for typus to improve symptoms in patients in German asylums.[64] Associative evidence is strong, with increased levels of inflammatory cytokines, including interleukin 6 (IL-6), tumour necrosis factor α (TNFα), and C-reactive protein (CRP), consistently reported to be higher in patients with depression than in control individuals. Causality has been inferred by both experimental design (eg, inducing a state of inflammation can bring depressive symptoms, primarily anhedonia, dysphoria, and lethargy) and in Mendelian randomisation studies of IL-6. Mechanistic explanations are that early life stress and environmental stressors lead to increased levels of pro-inflammatory cytokines, which, in turn, act on secondary actors (eg, prostaglandins), activate microglia, and (via the tryptophan and kynurenine system) affect the glutamatergic pathway and other pathways (figure 3). There have been many trials of anti-inflammatory agents in depression.

Bai and colleagues[65] did a systemantic review and meta-analysis of the effficacy and safety of anti-inflammatory agents for the treatment of MDD with a total sample of 1610 participants. Overall, treatments, including celecoxib (a cyclooxygenase-2 inhibitor) and other non-steroidal anti-inflammatory agents, omega 3 fatty acids, and statins, had a beneficial effect with a reduction in depressive symptoms in monotherapy or as an adjunct to antidepressant medication. However, effect sizes were moderate and gave a small pooled relative risk; publication bias and mixed quality of studies was also highlighted.[66] High-quality studies often show less significant or negative effects of anti-inflammatory agents on depression score. In a rigorous double-blind, 12-week trial of celecoxib (n=66), it did not have a superior effect to placebo.[67] A large, multicentre, population-based (n=19 114 participants with depression), double-blind, placebo-controlled trial of 100 mg aspirin once per day versus placebo showed that individuals taking aspirin for 4·7 years had a significant, although small, increase in depression scores.[68]

Minocycline is a tetracycline antibiotic with anti-inflammatory and GABA modulating effects. Although in schizophrenia there are negative results for minocycline in high-quality trials,[69] there is better primary evidence of its efficacy in depression, including the Stanley-funded, multicentre, 3-month, double-blinded RCT of minocycline versus celecoxib[67] and pooled meta-analysis.[65] Providing anti-inflammatory agents to patients with evidence of immune activation might be necessary and is the logical next stage of testing the potential effect of anti-inflammatory treatments. In 2021, Nettis and colleagues[70] reported a significant treatment effect of minocycline in patients with depression who had elevated CRP levels of more than 3 mg/L and a CRP threshold to distinguish responders from non-responders of 2·8 mg/L. Further studies targeting anti-inflammatory agents in patients with evidence of inflammation are needed.

Psychedelics

Clinical and research interest in psychedelics was sparked by lysergide, which was used widely in clinical practice throughout the 1950s and early 1960s.[71] Despite intense interest in the clinical effects of psychedelics (eg, lysergide, psilocybin, dimethyltryptamine, and mescaline), in 1967 they were classified under Schedule 1 of the UN convention on drugs, meaning they were deemed to have no accepted medical use and substantial potential for harm and dependence.[72] The important component of these so-called classic psychedelics is their agonist actions at the serotonin 2A receptor subtype (5-HT2AR).[73] However, their influence and antidepressant mechanism can be thought of as acting at various levels from this agonism to increased plasticity and brain entropy, which might lead to the relaxation of high-level beliefs.[71] Network cartography analyses indicate that receptor-rich, high-order functional networks with increased 5-HT2AR (eg, the default mode and the executive and salience network) become more functionally interconnected and flexible after psilocybin treatment compared with before treatment.[74]

A small number of studies have investigated the efficacy of psychedelics and, until the past 5 years, there were few RCTs of psychedelics in major depression. In a small, randomised trial (n=29) of people with TRD, one dose of freeze-dried ayahuasca brew (1·1 mg/kg of dimethyltryptamine) was compared with placebo.[75] Significant group differences in reduction of depressive symptoms were apparent after 7 days in favour of ayahuasca (p=0·019, d=0·98, 95% CI 0·21–1·75) compared with placebo, as well as in clinical response (57% *vs* 20%; p=0·04), although not in remission (43% *vs* 13%; p=0·07). An open-label, uncontrolled trial[76] (n=17) also showed significant decreases in depression

scores in patients with recurrent depression after ayahuasca (p<0·001) for up to 3 weeks.

In an RCT of 24 patients with primary MDD who were not taking antidepressants, patients were given two oral doses of psilocybin—initially 20 mg for every 70 kg of weight of an individual, then 30 mg for every 70 kg of weight of an individual 1–2 weeks later—in the context of receiving supportive psychotherapy (approximately 11 h).[77] The effect on reduction of depressive symptoms was significant and the effect sizes were large 1 week after the second dose (d=2·5, 95% CI 1·4–3·5, p<0·001) and 4 weeks after the second dose (d=2·6, 95% CI 1·5–3·7, p<0·001). An open-label clinical trial of 20 patients with TRD[78] also showed significant improvements in depressive symptom score at follow-up after 1 week, 5 weeks, 3 month, and 6 months. Subgroup analysis from a systematic review[79] using data from both of these studies concluded that the antidepressant effects of psilocybin were highly significant (Hedges' g=2·190, 95% CI 1·42–2·96, p<0·001) in patients with depression, with it being more effective in primary MDD than in secondary MDD in people with life-threatening physical issues, such as cancer.

Results from a phase 2, double-blind RCT comparing the efficacy of psilocybin with that of escitalopram in addition to psychological support (ie, not formal psychotherapy) in 59 patients with MDD were published in 2021.[80] Participants in the psilocybin group were given two doses of 25 mg psilocybin, first on day 1 and again 3 weeks later, alongside a placebo tablet once per day for 6 weeks. The escitalopram group were given a placebo dose, not thought to have significant psychotropic effect, of psilocybin of 1 mg on day 1 and again 3 weeks later, alongside a tablet of escitalopram 10 mg once per day for the first 3 weeks and a tablet of escitalopram 20 mg once per day for the final 3 weeks. Depressive symptoms, the primary outcome, were not significantly different between the two groups at the endpoint. In 2022, a large, international, phase 2b, double-blind RCT compared the safety and efficacy of COMP360 psilocybin at doses of 25 mg or 10 mg with doses of 1 mg in 233 patients with TRD after 2 weeks of a clinical wash-out period of their previous antidepressant. At 3 weeks after randomisation, 36% of the 25 mg COMP360 group compared with 18% of the 1 mg group had responded, and 29% of the 25 mg COMP360 group compared with 7% of the 1 mg group had remitted.[81]

In all studies assessing psilocybin, including in secondary MDD, it was well tolerated. The medication is usually administered during a procedure that incorporates psychoeducation about the possible effects of the medication, which lasts for approximately 8 h. Importantly, there are also a number of early-stage controlled trials that investigate the use of psilocybin in anxiety, depression, and so-called existential distress in terminal care, and have shown positive effects.[82] This so-called existential distress might be the area in which use is sanctioned the soonest.

Current research into the therapeutic uses of psychedelics in depression shows promising preliminary results. However, trials are still in the relatively early stages. Further research, specifically large phase 2 and phase 3 trials, is needed.

Other agents

Photobiomodulation is a novel device treatment based on non-retinal exposure to light. It is based on the idea that near infrared radiation and red light can be absorbed through the scalp skin and by mitochondrion chromophores that are known to be biologically active. A review suggested some positive results in improving depressive symptoms both in animal models and in humans, but nearly all studies lacked a control group.[83]

Pimavanserin has been licenced in the USA for the treatment of psychotic symptoms in people with Parkinson's disease. The agent has no appreciable action on D2 dopamine receptors but is an antagonist at the 5-hydroxytryptamine 2A (5-HT2A) and 5-HT2C receptors. When investigated in the CLARITY trial,[84] its addition to an antidepressant in people with TRD led to greater improvement in overall depression severity than placebo. Pimavanserin augmentation also led to a higher degree of treatment response or remission than placebo. The agent seemed particularly useful for sexual dysfunction, reducing hypersomnia, and irritability in people with depression. However, a phase 3 trial did not show a significant effect of pimavanserin.[85]

Precision medicine in the treatment of major depression

Replicability in large controlled trials is required for clinical use of any new treatment. However, substantial heterogeneity exists in current evidence. One issue that could have an effect on clinical utility is the heterogeneity of MDD itself. Because of the breadth of the diagnostic criteria, two individuals could have a diagnosis of MDD but share no common symptoms. Thus, strategies to develop improved treatments for MDD include stratification of subgroups and prediction of pharmacological response and outcomes, with objective and replicable psychosocial or neurobiological measures used to make treatment decisions. Data science approaches are essential to this endeavor.[86] However, the methods for predicting treatment response in MDD are still underdeveloped. A review of 12 prognostic model studies examining recovery or remission from MDD revealed overall poor predictive performance and many studies without sufficient external validation.[87] Models investigating treatment response to individual pharmacotherapy are somewhat more promising than those currently developed to predict recovery or remission. For example, the PREDICT trial tested the effectiveness of a clinical symptom-based algorithm to guide treatment versus unguided care for depression. The algorithm-guided care group did not have a higher rate of response to

	Class	Summary of current evidence	Effect size or OR (CI)	Category of evidence
Intravenous ketamine	NMDA modulators	A systematic review and meta-analysis of seven RCTs and 12 open-label trials showed a positive effect of ketamine on MDD[13]	Pooled OR at 7 days 6·33 (95% CI 3·33 to 12·05)	1
Intranasal esketamine	NMDA modulators	A systematic review[19] of five RCTs contained three RCTs that assessed outcome at 28 days of treatment (one showed a significant positive effect), one relapse-prevention study that showed a positive effect, and one open-label, long-term trial that showed a positive effect of esketamine on TRD	For the 28-day outcome studies, significant LSMD of MADRS score –4·0 (95% CI –7·31 to –0·64), p=0·02,[16] and non-significant LSMDs of MADRS score –3·2 (95% CI –6·88 to 0·45), p=0·002[30] and –3·6 (95% CI –7·20 to 0·07), p=0·059;[28] for the relapse-prevention study, risk of relapse HR 0·49 (95% CI 0·29 to 0·84), p=0·003[18]	1
Dextromethorphan and bupropion	NMDA modulators	One phase 2 trial[34] and one phase 3 trial[35] showed positive effects of augmentation in treatment-resistant depression	Phase 2 trial LSMD of MADRS score at 6 weeks of treatment –5·2 (95% CI –9·3 to –1·1); phase 3 trial at 6 weeks of treatment LSMD of MADRS score –3·87 (95% CI –6·36 to –1·39), p=0·002	2
Esmethadone	NMDA modulators	One phase 2a trial showed a positive effect of augmentation in MDD[38]	LSMD of MADRS score at 14 days –10·4 (90% CI –16·1 to –4·6), p=0·0039	2
rTMS (multiple modalities)	Brain stimulation	Nine meta-analyses of 58 primary studies showed a positive effect in treatment-resistant depression[40]	rTMS modalities were more effective than sham treatment for all outcomes; absolute relative risk reduction 23% (95% CI 15% to 32%), NNT 4	1
tDCS	Brain stimulation	A meta-analysis of eight RCTs showed a positive effect of tDCS on MDD[55]	OR 1·96 (95% CI 1·30 to 2·95)	1
Deep brain stimulation	Brain stimulation	A meta-analysis of 14 studies—all small and many not randomised—showed a positive effect of deep brain stimulation regardless of location of stimulation; one RCT of deep brain stimulation targeting the ventral capsule and ventral striatum showed no significant difference in response rates in TRD[58]	For the RCT, change in MADRS score in the active treatment group was 8·0 points (SD 13·7; 19·6% to 34·9% improvement) and change in MADRS score in the sham treatment group was 9·1 points (SD 10·6; 24·6% to 28·8% improvement)	2
Brexanolone	GABA modulators	Three RCTs[61,62] showed a positive effect in post-partum depression	For one RCT, mean difference after 60 h of treatment (HAM-D) –12·2 (95% CI –20·77 to –3·67), p=0·0075, effect size 1·2; for another RCT, LSMD (HAM-D) after 60 h of treatment –5·5 (95% CI –8·8 to –2·2), p=0·0013; for the third RCT LSMD (HAM-D) after 60 h of treatment –2·5 (95% CI –4·5 to –0·5), p=0·0160	2
Glucosamine	GABA modulators	A single, open-label, pilot study showed no significant effect of glucosamine on MDD[63]	Significant change in MADRS score after 2 and 4 week of treatment F=15·80, df=2·18, p<0·001; HAM-D F=14·42, df=2·18, p<0·001; magnitude of improvement was small and there was no significant change in global improvement scores	3
Omega-3 unsaturated fatty acid	Anti-inflammatory agents	A meta-analysis of 12 RCTs showed a positive effect of omega-3 unsaturated fatty acid on MDD[65]	SMD –0·35 (95% CI –0·60 to –0·09), p=0·008; there was moderate study heterogeneity	1
Minocycline	Anti-inflammatory agents	A meta-analysis of three RCTs showed a positive effect of minocycline on MDD[65]	SMD –0·79 (95% CI –1·29 to –0·28), p=0·002; there was moderate study heterogeneity	1
Statins (eg, lorvastatin, atorvastatin, and simvastatin)	Anti-inflammatory agents	A meta-analysis of three RCTs showed a positive effect of statins on MDD when administered with an SSRI;[65] a different meta-analysis of ten studies of statins compared with placebo had high heterogeneity and eight studies with high risk of bias, but showed a positive effect of statins on depressive symptoms in MDD[91]	SMD –0·65 (95% CI –0·96 to –0·33), p<0·0001; there was low study heterogeneity; SMD –0·796 (95% CI –1·107, –0·486), p=0·0001	1
Celecoxib	Anti-inflammatory agents	A meta-analysis of four RCTs[65] showed a positive effect of celecoxib on MDD when administered with an SSRI; with small pooled relative risk, publication bias and mixed quality were highlighted; an RCT showed no benefit of celecoxib over a placebo[67]	For the meta-analysis, SMD –0·76 (95% CI –1·14 to –0·39), p<0·0001; there was low study heterogeneity; for the RCT, mean adjusted difference (HAM-D) at 12 weeks follow-up 1·48 (95% CI –0·41 to 3·36), p=0·123	1
Aspirin	Anti-inflammatory agents	A large RCT of depression prevention in individuals older than 65 years in the USA and Australia showed a small negative effect of aspirin on the risk of developing MDD[68]	HR during 5 years follow-up 1·02 (95% CI 0·96 to 1·08), p=0·54	1
Ayahuasca	Psychedelics	One small RCT[75] and one open-label study showed a positive effect of ayahuasca on TRD	For the RCT, on day 7 of follow-up after a single dose d=0·98 (95% CI 0·21 to 1·75), p=0·019	2
Psilocybin	Psychedelics	One RCT and one open-label study in a meta-analysis[79] showed a positive effect of psilocybin on TRD; one RCT comparing psilocybin with escitalopram showed no superiority;[80] one phase 2 RCT showed a positive effect of psilocybin on MDD[81]	For the meta-analysis, Hedges' g=2·190 (1·42 to 2·96), p<0·001; for the RCT, between-group difference after 6 weeks of follow-up 2·0 (–5·0 to 0·9), p=0·17; for the phase 2 RCT, remission rates after 12 weeks of follow-up were 29% in the 25 mg of psilocybin group compared with 7% in the 1 mg of psilocybin group	2

GABA=γ-amino butyric acid. HR=hazard ratio. HAM-D=Hamilton Depression Rating Scale. LSMD=least square mean difference. MADRS=Montgomery-Åsberg Depression Rating Scale. MDD=major depressive disorder. NMDA=N-methyl-D-aspartate. NNT=number needed to treat. OR=odds ratio. RCT=randomised controlled trial. rTMS=repetitive transcranial magnetic stimulation. SMD=standardised mean difference. SSRI=selective serotonin reuptake inhibitor. tDCS=transcranial direct current stimulation. TRD=treatment-resistant depression. There are four categories of evidence for causal relationships and treatment.[92] 1=evidence from meta-analysis of RCTs; at least one large, good-quality RCT; or replicated, smaller RCTs. 2=evidence from small, non-replicated RCTs; at least one controlled study without randomisation; or evidence from at least one other type of quasi-experimental study. 3=evidence from non-experimental descriptive studies, such as uncontrolled, comparative, correlation, and case-control studies. 4=evidence from expert committee reports, opinions, or clinical experience of respected experts.

Table 2: **Summary of evidence for various drugs and interventions**

antidepressant than treatment as usual, but did have reduced anxiety and better functional outcome at week 24.[88]

Challenges

Fundamental challenges remain to be addressed to ensure effective treatments become widely used in clinical practice. First, the durability of effect of several interventions requires further investigation, including improved characterisation of factors that predict it or that might prevent it. The effect, for example, of intravenous ketamine appears to be rapid, and thus potentially lifesaving. However, whether the model for ketamine in various forms of administration is continuous treatment in the medium term (eg, for months or years) or whether the brain is fundamentally changed by treatment is unclear, as is whether other antidepressants can be then be used in continuation. Other challenges include whether tolerance develops to NMDA modulators or psychedelics, and whether there is a high rate of relapse if the treatment is stopped (as is seen in other agents).[89] If psychedelics and NMDA modulators are to be administered in the long-term, further investigations are needed to establish the doses and frequency required.

Second, several lines of research are being pursued in isolation, whereas the mechanisms of action for various agents are overlapping and intricate. For example, low-level inflammation resulting from genomic effects, environmental effects, or a combination of both might result in effects on glutamate and excitation or inhibition, or could itself be an alternative effect. Treatment of inflammation could therefore be of importance. Evidence published in 2022 suggests inflammation might be more relevant to neurodevelopmental disorders or trans-diagnostic phenotypes with poor outcome.[90] Inter-disciplinary, transdiagnostic research across cellular, preclinical, and human studies is still necessary.

Third, major developments have been primarily in MDD and TRD in adults. The FDA approval of brexanolone for use in post-partum depression is a notable exception. A major future challenge is testing these new agents in older adults and in children and adolescents, in whom morbidity is an increasing challenge and prescribing is complex either because of a developing brain and changing physiology or because of multimorbidity, cognitive decline, and pre-existing pharmacology.

Fourth, the widespread use of many of these agents will need patients, clinicians, and health-care services to change the way they think, recognising medical treatment for MDD within a biopsychosocial approach. Many of these interventions (eg, rTMS) require specific equipment to be operated for laboratory diagnostic tests (eg, blood tests) and for medical monitoring, which may be representative of an increased need for neuroscientific knowledge. Thus, novel treatments might still be most acceptable for people with severe TRD.

Finally, there is concern from clinicians and patients about the potential for the misuse of several novel and emerging agents. Concerns are understandable because, for example, both psilocybin and ketamine are known to be misused agents. Data on dosing in medicinal products and how this differs to doses used by people who are misusing these substances are needed. Long-term registries might be needed for people taking medicines that are also used recreationally to fully understand the extent to which there are long-term dangers, if any.

Conclusion

The scientific and clinical community has made major progress in using and advancing mechanistic knowledge, developing new agents and testing them to improve the biological treatment of MDD (table 2). Important developments are that many agents have a rapid onset of action that will be clinically invaluable in various situations, and they might have improved tolerability. Many novel and emerging agents might be able to target people with depression that is difficult to treat, but there is a need for specific trials in this patient subgroup. This new evidence could bring hope for improved treatments. New agents have many neurochemical targets, consistent with neuroscientific knowledge of depression, and this knowledge can be used to inform further developments in the use of novel treatments in depression, which addresses a global need for improved treatment of depression.

Contributors

SM, RU, EP, and AHY developed the scope of this Review. SM led the writing of this Review. RU and EP contributed to the initial writing of this Review. EP searched the databases. EC retrieved articles and developed the figures. All authors contributed to various versions of this Review.

Declaration of interests

SM attended an educational event sponsored by Janssen in 2019. He is an unpaid council member of the British Association of Psychopharmacology. He has grants funded by the National Institute for Health and Care Research, UK Research and Innovation, the Medical Research Council, and the Wellcome Trust. RU receives speaker fees from Sunovion, Springer Heathcare, and Vitaris. She receives grant funding from the Medical Research Council (MR/S037675/1), the National Institute for Health and Care Research: Health Technology Assessment (NIHR 127700), and the National Institute of Mental Health (1U01MH124631–01). She is unpaid Honorary General Secretary of the British Association for Psychopharmacology and is the Deputy Editor of *The British Journal of Psychiatry*. In the past 3 years, TS has received grants from Compass Pathways and Merck. She is a consultant for Sunovion Pharmaceuticals, Merck Research Laboratories, Impel NeuroPharma, Intracellular Therapies, Servier (Australia), and Allergan. She receives royalties from American Psychiatric Association Publishing, Hogrefe Publishing, Jones and Bartlett, and Wolters Kluwer Health (UpToDate). She has financial interests with PsiloTec (stock options). She receives continuing medical education honoraria from the CME Institute (Physicians Postgraduate Press), CMEology, Medscape, and Novus Medical Education. AHY is employed by King's College London. He is an Honorary Consultant for South London and Maudsley NHS Foundation Trust (NHS UK) and is Deputy Editor of *BJPsych Open*. He receives payment for lectures from AstraZeneca, Eli Lilly, Lundbeck, Sunovion, Servier, Janssen, Allegan, Bionomics, Sumitomo Dainippon Pharma, COMPASS, Sage, and Novartis. He receives payment for being on advisory boards from Livanova, Janssen, COMPASS, Novartis,

and Neurocentrx. He is a consultant for Johnson & Johnson. He is a consultant to Livanova. He has received honoraria for attending advisory boards and presenting talks at meetings organised by LivaNova. He is the Principal Investigator in the Restore-Life VNS Global Prospective, Multi-center, Observational Post-market Study to Assess Short-, Mid- and Long-term Effectiveness and Efficiency of Vagus Nerve Stimulation Therapy (VNS Therapy) as Adjunctive Therapy in Real-world Patients with Difficult to Treat Depression (RESTORE-LIFE) registry study funded by Livanova, ESKETINTRD3004 ("An open-label, long-term, safety and efficacy study of intranasal esketamine in treatment-resistant depression."), "The effects of psilocybin on cognitive function in healthy participants.", and "The safety and efficacy of psilocybin in participants with treatment-resistant depression (P-TRD)". He is the UK Chief Investigator for Novartis Major Depressive Disorder MIJ821A12201. He receives grant funding from the National Institute of Mental Health (USA), the Canadian Institutes of Health Research, the National Association for Research on Schizophrenia And Depression (USA), the Stanley Medical Research Institute (USA), the Medical Research Council (UK), the Wellcome Trust (UK), the Royal College of Physicians, the British Medical Association (UK), the UBC-VGH Foundation (Canada), the WEDC (Canada), the CCS Depression Research Fund (Canada), Michael Smith Health Research BC (Canada), the National Institute for Health and Care Research (UK), and Janssen (UK). EC and EP declare no competing interests.

Acknowledgments

We thank Connor Dunleavy (University of Birmingham, UK) for assistance with the figures in this Review.

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