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NOVEL AND EMERGING TREATMENT FOR MAJOR DEPRESSION

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Abstract

Depression is common, costly, debilitating, and associated with increased risk of suicide. It is one of the leading global public health problems. Whilst existing available pharmacological treatments can be effective, onset of action can take weeks, side effects are common, and recovery can require treatment with multiple different agents. Although psycho-social interventions may also be recommended, more effective treatments than those that are currently available are needed for patients with moderate or severe depression. In recent years, treatment trials have developed and tested a plethora of new, more targeted interventions. In this *Therapeutics* paper we review novel and emerging biological treatments for major depression, linking them to putative significant brain/body mechanisms, and highlight how close or far they might be from routine clinical use.

Introduction

Depression is a major global mental health challenge and is *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, depression starts in mid to late adolescence with median 12 month prevalence in this age group being 4-5%[3]. Major depressive disorder (MDD) damages education, relationships, employment and is prospectively associated with obesity, cardiac disease, and with early death, including suicide[4-6]. The financial costs are very large and closely linked to working days lost, reduced productivity and absenteeism. Functional impacts are particularly significant in adults where comorbidity with physical health problems commonly complicates the picture further.

Contemporaneous biomedical models of depression conceptualise this 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 (serotonin, noradrenaline and dopamine). Although guidelines recommend a comprehensive biopsychosocial approach, and evidence suggests psychological interventions, social support and exercise are important, treatment with medication is often essential in moderate or severe depression. Whilst antidepressants are effective, a third to half of people with MDD do not respond to multiple anti-depressants[9, 10] and a higher proportion may only obtain a partial response. People who do not respond to two trials of anti-depressants are commonly categorised as having treatment resistant depression (TRD). Typically, individuals must wait at least 4 weeks before obtaining a potential response to current anti-depressants, and side effects such as sexual dysfunction, loss of libido, headache, gastrointestinal symptoms, anxiety and agitation are common.

Thus, 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, and with the potential for greater effectiveness at least in the people in whom current anti-depressants have failed, and with better tolerability. We aimed to provide an expert review of novel biological treatments, using a systematic approach to highlight the best currently available evidence, with a particular emphasis on mechanism of effect and which depressed populations new treatments may ultimately be clinically useful. Although not a formal systematic review, we

outline search terms and strategy in online materials. Table 1 outlines potential target by emerging treatment and proximity to routine use and Table 2 a summary of the current level of evidence for emerging treatments.

N-methyl-D-aspartate (NMDA) modulators

Glutamate functioning is known to be disturbed in brain areas linked to depression[11]. It is the commonest brain excitatory neurotransmitter and levels are increased by chronic stress. This glutamatergic upsurge can decrease synapse connectivity and result in deficits in GABA functioning, the most abundant inhibitory brain neurotransmitter. Both glutamate and GABA, or perhaps the balance between them in different brain areas are thought to be one of the final common pathways in depression, as well as the focus of antidepressant actions.

Ketamine

Research on ketamine has rapidly expanded 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 NMDA receptor in the brain as shown in ***Figure 1.*** Ketamine also acts to increase Brain-Derived Neurotrophic Factor's (BDNF) translation[12] a key agent involved in neural plasticity and known to be abnormal in depression. Reported areas of brain action for Ketamine as well as other agents in this review are shown in ***Figure 2.*** Ketamine in clinical use for depression can be administered intravenously (I.V), intramuscularly (I.M), in tablet form as well as intranasally (Esketamine now licenced by the FDA, though not yet sanctioned by NICE). I.V dosage is commonly 0.5mg/kg delivered over 30-40 minutes with blood pressure, heart rate and temperature monitoring and can be administered alone or as an adjunct to another antidepressant.

Multiple meta-analyses have assessed ketamine efficacy with the majority focussing on its use in TRD. Ketamine infusion appears to be rapidly effective in alleviating depressive symptoms in TRD. In placebo controlled RCTs depression scores are significantly reduced compared to placebo with a standardized mean difference (SMD) of 0.68 (95% Confidence Interval (CI):0.46-0.9) after 24 hours (available from 7 RCTs), but with a fairly rapid reduction

of effect over the following week (SMD=0.77 at 24 hours vs 0.49 at 7 days post-infusion). A systematic review based on 28 studies from 2009-2019, but with 19 being suitable for meta-analysis evaluating the efficacy of ketamine infusions in people with TRD indicatesefficacyin clinical response (pooled Odds Ratio (OR):6.33; CI:3.33-12.05) at 7 days based on 7 studies though the largest response was found after 24 hours. Data from 4 studies indicated an effect on clinical remission favouring ketamine (OR:5.11 (CI:2.15-12.17) at 24 hours post-infusion with reductions of effectiveness at 7 days[13]. There may be some level of sustained anti-depressant effect post-treatment for up to 6 weeks[14], though the large effect size (g = −1.36, 95% CI: −2.69 to −0.04, t4 = −2.85, p = .05) reported in this meta-analysis of the effectiveness of ketamine was based on only 5 studies, in which there was a high degree of heterogeneity and Eggers test for publication bias could not be completed because of insufficient studies..

A similar pattern of effect, but from evidence which is subject to a range of bias, has been found with intranasal Esketamine [15] in people nonresponsive to at least 2 previous anti-depressants and given as an adjunct to a recognized anti-depressant. Treatment is usually twice weekly. One (TRANFORM-2)[16] of three short term clinical trials over 28 days found Esketamine to improve depressive symptoms when added to an oral antidepressant, in comparison to placebo (least squared mean difference (LSMD) of −4.0 (standard error (SE) = 1.69, 95% CI = −7.31 to −0.64, p = 0.020). Whilst the LSMD was of a comparable order in TRANFORM 1 (-3.2) and 3 (-3.6), a statistically significant difference was not found. One (TRANFORM-3)[17] of the negative trials was in older people aged 65 years and over. In the SUSTAIN 1 relapse prevention trial, in people who had responded to Esketamine, continued treatment in addition to an oral antidepressant increased time to relapse in comparison to placebo (log-rank P < .001, NNT, 4).[18] The SUSTAIN-2 open label longer term trial found a sustained effect over 1 year in those who respond [19,20]. The reduction in depressive symptoms can occur within a day[16]. 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 anti-depressant [18,20]. Phase II and phase III trials indicate that the effects of Esketamine are lost when the medication is stopped[21], not unlike effects that may be lost with cessation of other anti-depressants.

It is important to note that a recent overview of systematic reviews and meta-analyses[15] of the effectiveness of ketamine and Esketamine note that bias within individual studies have

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" using the AMSTAR-2 quality assessment. Therefore, results should be considered in this context.

In a large recently completed network meta-analysis (N=8282 TRD patients, only 116 allocated to NMDA medication) of augmenting agents, NMDA modulators were better than placebo (Effect Size (ES)= 0.91, 95% CI 0.67-1.16) in reducing depressive symptoms. Minocycline (an NMDA antagonist) appeared to have a particularly large ES. NMDA modulators had the highest chance of being an effective treatment[22]. A specific comparison with augmenting with anti-psychotics indicates add on intranasal Esketamine may be around twice as effective in reducing depressive symptoms [23].

In people with TRD undergoing ECT, there is low quality evidence (as determined by GRADE criteria) to indicate that Ketamine added to Propofol (a common anaesthetic) results in a rapid reduction of depressive symptoms within a single ECT session[24]. Whilst this signal is important given the high morbidity of people who are usually treated with ECT there is a lack of convincing evidence that Ketamine agents are an effective alternative to ECT in managing TRD[25]. The evidence that ketamine agents could reduce suicidality in people with MDD is far from clear and doubts remain about the stability, nature and persistence of any effect [15].

Therapeutics is a particularly difficult issue in adolescent depression with few agents shown to have a tangible action. A single available randomised trial (N=17) of Ketamine administered intravenously and using Midazolam as a control indicates an acute reduction of depressive symptoms (ES=0.78) at 24 hours in 13–17-year-olds with these gains maintained by day 14 follow-up. The main adverse effect was transient dissociation[26]. Longer term studies examining efficacy and side effects are urgently needed. The evidence in adults is more mixed with one positive[27] trial of subcutaneous Ketamine in people with TRD and one negative trial[28,29] of intranasal Ketamine. ***Table 1*** summarises in which depression population, Ketamine and other treatments have been studied, and also indicates the potential position in implementation for patient benefit.

Whilst depressive symptom reduction is clinically important, a return of functioning is a priority for patients. RCT evidence that Ketamine leads to improved functioning is limited, with analyses not completed in 2 trials because there was no difference in the primary depression endpoint [28,30]. A third study indicated a difference in functioning 4 weeks post-treatment, in comparison to placebo as measured by the Sheehan Disability Scale (ES: 0.48; CI: 0.17-0.78) which focusses on disruption of work / school life, social life, family responsibilities, days lost from work / school and days that the individual was unproductive [16].

Side effects with I.V Ketamine are typically described as "mild" but include drowsiness, dizziness, poor coordination, blurred vision and feeling strange or unreal. The commonest side effects people experience with intranasal Esketamine appear to be dissociation, headache, nausea, vertigo, altered sense of taste and sleepiness[15]. A robust review of side effects has highlighted potential selective reporting bias in existing studies[31]. There is also concern over abuse, but the cost of prescribed Ketamine may 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 may be important in the landscape 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 US for Pseudobulbar Affect. On a background of positive results in rodent models, clinical studies including phase II[34] trials indicate better remission rates in people with TRD at 6 weeks with combined dextromethorphan and bupropion versus bupropion alone (47% vs. 16%). In the larger phase III GEMINI trial (N=327) [35,36] twice daily combination treatment resulted in a significant reduction in MADRS scores at week 1 and up to week 6 in comparison to placebo (week 1: −7.3 vs −4.9, p = 0.007; week 6: −16.6 vs −11.9, p = 0.002). The FDA have recently approved the dextromethorphan plus bupropion combination for the treatment of MDD.

Esmethadone

Esmethadone is an opioid inactive isomer of racemic methadone which binds to the NMDA receptor with low affinity and potency. Esmethadone's potential anti-depressant action could be a function of increasing plasma BDNF[37] and/ or changing synaptic plasticity via the NMDA receptor complex. It is reported not to have clinically meaningful opioid effects and is not considered to have significant drug abuse liability. Whilst the agent also has affinity for monoamine receptors, the extent of this binding makes monoamine receptor action an unlikely primary mechanism. In a phase IIA placebo controlled double blind trial in patients with MDD who had not responded to 1-3 anti-depressants in the current episode and who were taking an SSRI, SNRI or Bupropion there was a significant improvement in depressive symptoms on day 4 and 7 of daily oral Esmethadone, which was sustained a week after the last dose. The effect size was large (0.7-1) [38] and common side effects were headache, constipation, nausea, and somnolence.

Brain stimulation

Repetitive transcranial magnetic stimulation (rTMS)

Transcranial Magnetic Stimulation (TMS) is a form of non-invasive brain stimulation which doesn't require an anaesthetic, with the TMS machine generating a magnetic field targeting stimulation of particular brain areas. This in turn can lead to changes in neuronal excitability triggering downstream effects between cortical and subcortical structures. Areas particularly relevant are the left dorsolateral prefrontal cortex (DLPFC) which is known to be underactive in depression and linked to treatment resistance, and the right prefrontal cortex (PFC) which may be over-active in people with depression. The left DLPFC is typically repeatedly stimulated with high frequency rTMS, whereas the right PFC typically using low frequency TMS. The treatment usually involves 30–45-minute treatment episodes per day for 4 weeks (at least). As might be expected placebo response is known to be large but is lower in people with more severe depression and is not linked to gender or age [39].

A recent health technology assessment review from Ontario Canada assessed data from 9 systematic reviews and 58 primary studies reporting on the effectiveness of rTMS in adults with TRD compared to sham. Whilst there are a variety of different TMS modalities, they concluded that there was evidence that rTMS is an effective treatment, but that different rTMS modalities do not differ in effectiveness[40]. The meta-analysis investigating the response rate compared to sham showed that the absolute risk reduction was approximately 23% (CI: 15%–32%), and number needed to treat (NNT) is 4. These results have been replicated in other reviews [41], which also generally suggest that rTMS is not as effective as ECT in this patient population.

Many trials indicate no side effect differences between sham and active treatment which would at least on the face of it seem unlikely 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 commonest reported side effects, followed by fatigue, pain, dizziness, insomnia, eye and nasal problems, and GI issues. Good quality data on whether rTMS leads to emergent hypomania in people with unipolar depression is not available but current evidence indicates not [42]. There is clearer evidence that rTMS can trigger affective switches in people with bipolar disorder [43].

Researchers have investigated various ways in which to reduce the treatment burden of rTMS. Accelerated protocols have tested more than once daily administration of rTMS. Though the quality of the evidence is not high, it suggests that effectiveness with 10 Hz high frequency rTMS using 2-15 sessions per day over a few days is not inferior to once-a-day protocols[44,45] with response rates of 36-56% in people with depression. With recently FDA approved theta burst stimulation (e.g 50Hz) treatment sessions typically have a shorter duration with lower stimulation intensity offering an acceptability advantage. Data from RCTs (N = 294) and 4 uncontrolled clinical trials (N = 297) suggests a pooled significant effect on response (ES: 0.38; CI: 0.29–0.48) and on remission (ES: 0.20, CI: 0.13–0.29)[46].

The impacts of rTMS appear to be durable over 1 year with meta-analysis suggesting that amongst people who have initially responded (n=247, 9 studies), 46.3% (CI: 32.6-60.7) have a sustained response at 1 year. Female sex and being in receipt of maintenance treatment was

associated with higher durability [47]. Comorbid anxiety symptoms, and incomplete response to rTMS may be associated with relapse after rTMS [48].

One area where rTMS could potentially be invaluable is the treatment of depression in older adults. The prospect of a biological treatment which doesn't interfere with medication for physical comorbidity could be invaluable. Out of 7 RCTs including a comparison to sham, most with small samples, 3 found a significant difference, though the endpoint for most was 2 weeks[49]. The response rate from both RCTs and uncontrolled studies was highly variable ranging from 6-54%.

In peri-partum (gestational period and up to 4 weeks after delivery) depression, meta-analysis indicates a positive effect (ES: 1.394; CI: 0.94–1.84) with little in the way of severe side effects to mother or baby[50]. This is particularly important as many women do not want to take medication during pregnancy because of concerns over the impact on the foetus. In postpartum depression, results are promising but higher quality evidence is still needed [51]. Similarly there appears to be a signal of effectiveness for using rTMS in the treatment of adolescent depression, though only from open label studies and non-controlled trials [52]. The only RCT with a sham in adolescent depression indicates rTMS did not differ significantly from sham in this population[53].

Transcranial direct current stimulation (tDCS)

tDCS involves applying a weak electrical current over the scalp across an anode and cathode often by the use of a cap. Treatment usually involves 5-10 stimulations per day, for up to 6 weeks. The sham response is large[54]. However a recent individual patient data meta-analysis incorporating 9 studies and 572 participants indicates tDCS was significantly better than sham 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 and shams suggest good acceptability. tDCS is considered to be safe and well tolerated, but reported side effects in case reports do include 1 case of seizure in an individual with pre-existing epilepsy, and skin burns under the anode and cathode. Evidence also indicates an overall rate of 3.3% risk of emergent mania in people with unipolar depression and an increased odds of 5.01 (CI:1.37-

18.26, p=0.015) and a pooled risk difference of 0.031 (0.011-0.050, p=0.002) in comparison to sham [56].

Deep brain stimulation (DBS)

DBS is a neuro-surgical intervention investigated for severe TRD. Studies have investigated stimulation of a variety of brain regions including the ventral capsule / ventral striatum, nucleus accumbens and subcallosal cingulate gyrus. Syntheses of small clinical trials, many without randomisation suggests a potential benefit [57] but this is independent of stimulation target. Side effects include surgery related (e.g. swollen eye), somatic (e.g. headaches) and psychiatric (e.g worsening of depression and agitation). Despite this meta-analytic evidence, a well conducted RCT using a sham control failed to find an effect on reducing depression with DBS, specifically targeting the ventral capsule/ventral striatum [58].

Gamma-amino butyric acid (GABA) modulators

Cognitive distortions including episodic memory, impaired learning, attention, negative bias and poor problem solving are all common features of depression. Evidence has highlighted the potential of GABA inhibition in such cognitive distortions[59]. In a magnetic resonance spectroscopy imaging study (1H-MRS), reduced GABA is apparent in MDD patients with anhedonia[60].

Allopregnanolone, a progesterone metabolite, is a positive modulator of the GABA receptor which exerts effects at both synaptic and extra synaptic levels. Primarily studied in postpartum depression three double blind RCTs have shown an allopregnanolone infusion gave a rapid reduction in anxiety and depression in women with postpartum depression [61,62]. FDA approval for Brexanolone (the therapeutic preparation of allopregnanolone) was granted in 2020 in the USA.

Glucosamine hydrochloride 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. A 4-week small open label pilot study of glucosamine [63] as monotherapy did not demonstrate an effect in people with depression. No adverse effects were noted but more definitive research is needed.

Anti-inflammatory agents

The proposal that immune dysfunction, or more specifically non-resolving low-level inflammation, may 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 residing in German asylums [64]. Associative evidence is strong, with increased levels of inflammatory cytokines including interleukin (IL) 6, TNFa and C-reactive protein (CRP) consistently reported to be higher in patients with depression compared to controls. Causality has been inferred by both experimental design: inducing a state of inflammation can bring depressive symptoms, primarily anhedonia, dysphoria and lethargy, and in mendelian randomisation studies of IL6. Mechanistic explanations are that early life stress, and environmental stressors promote increased levels of pro-inflammatory cytokines which in turn act on secondary actors including prostaglandins, activate microglia and via the tryptophan/kynurenine system effect glutamatergic and other pathways; ***see figure 3.*** It is unsurprising then that there have been many anti-inflammatory trials targeting depression.

Bai et al conducted a systematic review and meta-analysis citing 37 studies with a total sample of over 1600 participants[65]. Overall treatments, including celecoxib (a COX-2 inhibitor) and other NSAIDS, omega 3 fatty acids and statins, had a beneficial effect with a reduction in depressive symptoms in monotherapy or as an adjunct. However, effect sizes were moderate and gave a small pooled relative risk; publication bias and mixed quality of studies has also been highlighted[66]. Higher quality studies often show less significant, or indeed negative effects. In a rigorous double blind 12-week trial of Celecoxib (n=66), it did not have a superior effect to placebo [67]. A large multi-centre, population-based (N>1800 depressed participants), double-blind, placebo-controlled trial of 100mg aspirin daily vs placebo (the ASPREE-D study) found those taking aspirin over 4.7 years had a significant (although small) *increase* in depressive scores[68].

Minocycline is a tetracycline antibiotic with anti-inflammatory and GABA modulating effect. Whilst in schizophrenia there are negative results for minocycline in high quality trials [69], there is better primary evidence of efficacy in depression, including the Stanley funded multicentre 3 month double blinded RCT of minocycline or celecoxib [67], and pooled in meta-analysis[65]. Targeting anti-inflammatory agents to patients with evidence of immune activation may be necessary and is a logical step. Nettis et al [70] recently reported significant treatment effect with minocycline in patients with depression who had elevated CRP levels of >3mg/l and a CRP threshold to distinguish responders from non-responders of 2.8mg/l.

Psychedelics

Clinical and research interest in psychedelics was sparked by lysergic acid diethylamide (LSD) and it was used widely in clinical practice throughout the 1950s and early 1960s[71] . Despite intense interest of the clinical effects of psychedelics (LSD, psilocybin, N,N-dimethyltryptamine and mescaline), in 1967 they were classified under Schedule 1 of the United Nations convention on drugs, meaning they were deemed to have no accepted medical use and significant potential for harm and dependence[72]. The hallmark of the 'classic psychedelics' is their agonist actions at the serotonin 2A receptor subtype (5-HT2AR)[73]. However, it has been suggested their influence and antidepressant mechanism can be thought of as acting at various levels ranging from this agonism coupled with heightened plasticity and brain entropy, which may ultimately result in the relaxation of high-level beliefs[71]. Network cartography analyses indicate that 5-HT2A receptor-rich higher-order functional networks (e.g the default mode, executive and salience network) become more functionally interconnected and flexible after psilocybin treatment[74].

A limited number of studies have investigated efficacy and until very recently there were few RCTs of psychedelics in major depression. In a relatively small randomised trial (n=29) sampling people with TRD, one dose of freeze-dried ayahuasca brew (1.1 mg/kg n,n-DMT) was compared to placebo[75]. Significant group differences in reduction of depressive symptoms were apparent at day 7 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), though

not of remission (43% vs. 13%; p = 0.07). A further open label uncontrolled trial[76] (N=17) also showed significant decreases in depression scores (p<0.001) for up to 3 weeks.

In a RCT of 24 patients with primary MDD, who were not currently taking antidepressants, participants were given 2 oral doses of psilocybin initially 20mg/70kg and then a higher 30mg/70kg approximately 1-2 weeks later[77] in the context of receiving supportive psychotherapy (approximately 11 hours). Impact on reduction of depressive symptoms was significant and the effect sizes were large at 1 week post second dose (d = 2.5; 95% CI, 1.4-3.5; P < .001) and 4 weeks post second dose (Cohen d = 2.6; 95% CI, 1.5-3.7; P < .001). A further open label clinical trial of 20 patients with TRD[78] also showed significant improvements in depressive symptom score at week 1 and 5 and at 3 and 6 month follow-up. Sub group analysis from a systematic review [79] drawing from both these studies concluded that the antidepressant effects were highly significant (Hedges' g=2.190; CI= 1.42-2.96, p<0.001) in patients with depression, with it being more effective in primary MDD as opposed to secondary (in the context of physical health problems).

More recently results from a phase II, double blind RCT comparing efficacy of psilocybin with that of escitalopram in addition to psychological support in 59 patients with MDD[80] have been published. The psilocybin group were given two doses of 25mg psilocybin, first on day 1 and again 3 weeks after along with a placebo tablet daily for 6 weeks. The escitalopram group were given a presumed placebo dose of psilocybin of 1mg on day 1, and again 3 weeks later and daily tablet of escitalopram 10mg for the first 3 weeks and 20mg for the final 3 weeks. Depressive symptoms, the primary outcome was not significantly different at the endpoint. Very recently, a large international phase 11b double-blind RCT compared safety and efficacy of COMP360 psilocybin at 25mg or 10mg to 1mg in 233 patients with TRD after a 2 week wash out of previous antidepressant. At 3 weeks post randomisation, 36% of the 25mg COMP360 group compared to 18% of the 1mg group had responded. And 29% compared to 7% had remitted. [81]

Across all studies using psilocybin, (including secondary MDD) it was well tolerated. The medication is usually administered during a procedure that incorporates psychoeducation about the possible effects of the medication, and that lasts approximately 8 hours.

Importantly there are also a number of early stage controlled trials which investigate the use of psilocybin in anxiety, depression and "existential distress" in terminal care and have shown positive effects[82], and this therapeutic space may be where use is sanctioned soonest.

The current research into the therapeutic uses of psychedelic in depression show promising preliminary results, however, trials are still in relatively early stages. Further research and specifically further large phase II and III trials are needed.

Other agents on the horizon

Photobiomodulation is a novel device treatment based on nonretinal exposure to light. This is based on the idea that near infrared radiation and red light can be absorbed through the scalp skin and by mitochondrion chromophores which are known to be biologically active. A review in this area suggests some positive results in improving depressive symptoms both in animal models and in humans but nearly all studies lack a control group [83].

Pimavanserin tartrate has been licenced in the US for the treatment of psychotic symptoms in people with Parkinson's Disease. It has no appreciable action on D2 receptors but is an antagonist at the 5HT2a and 5-HT2c receptor. Investigated in the CLARITY trial its addition to an anti-depressant in people with TRD led to greater improvement in overall depression severity as compared to placebo. Pimavanserin augmentation also led to a higher degree of treatment response or remission compared to the placebo arm[84]. The agent seemed particular useful in tackling sexual dysfunction, reducing hypersomnia, and irritability in people with depression. However, a phase III trial did not demonstrate a significant effect [85].

Precision medicine in the treatment of major depression

Replicability in larger controlled trials is needed for clinical adoption of any new treatment, however it is clear from evidence above that significant heterogeneity exists in current evidence. One issue that may have an impact on this is the heterogeneity of MDD itself.

Indeed, given the breadth of the diagnostic criteria two or more individuals could have a diagnosis of MDD but share no common symptoms. Thus, one strategy to develop better treatments for MDD include stratification of subgroups, and prediction of pharmacological response and outcomes, moving away from 'one-size-fits-all approach' for treatment decisions by using objective and replicable psychosocial and/or neurobiological measures. Data science approaches are essential to this endeavor [86]. However, the methods for predicting treatment response in MDD is still in infancy. A review of 12 prognostic model studies examining recovery or remission from MDD revealed overall poor predictive performance and limited external validation [87]. Models investigating treatment response to individual pharmacotherapy are somewhat more promising; 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 antidepressant but did have reduced anxiety and better functional outcome at week 24 [88].

Key challenges

Fundamental questions remain to be addressed to ensure some of these effective treatments become widely used in clinical practice. Firstly, the durability of effect of several interventions requires further investigation, including better characterisation of factors that predict it, or are barriers to it. The impact for example of I.V. Ketamine appears to be rapid, and thus potentially lifesaving; however, it is less clear whether the model for Ketamine in whatever form of administration is continuous regular treatment in the medium term (many months and years), or whether the brain is fundamentally changed by treatment, and other anti-depressants can be used in its stead. Does tolerance develop to NMDA modulators or psychedelics, and if the treatment is withdrawn is there a high rate of relapse as with other agents[89]. If to be administered over the longer term investigations are required about what doses are required.

Secondly, a number of avenues are being pursued in isolation, whereas mechanisms are overlapping and intricate. For example, low level non resolving inflammation (resulting from genomic or environmental or a combination of both) may result in downstream impact on

glutamate and excitation / inhibition or may itself be alternative effect. Treatment of inflammation may therefore be of peripheral importance or more central. Indeed, recent evidence suggests inflammation may be more relevant to neurodevelopmental disorders or transdiagnostic phenotype with poorer outcome. Interdisciplinary, transdiagnostic research across cellular, preclinical and human studies are still much needed.

Third, major advancements have been primarily in MDD and TRD in adults. The FDA approval of Allopregnanolone 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 where morbidity is significant and prescribing especially complex either because of a developing brain and changing physiology or because of multi-morbidity, cognitive decline and pre-existing complex pharmacology.

Fourth, the widespread use of many of these agents will need a change in thinking of patients, clinicians and in the set-up of healthcare services, and a move towards recognising medical treatment for MDD within a biopsychosocial approach. This is because many of these interventions require equipment to be operated, lab work-up and medical monitoring, as well as a move towards a greater need for neuroscientific knowledge. This may be most acceptable for people with severe TRD.

Finally, there is a concern from clinicians and patients about the potential for abuse of a number of these novel and emerging agents. Concerns may be theoretically principled, given that for example psylocibin and ketamine are used as drugs of abuse. Much clearer data on dosing in medicinal products and how this differs to dosages used by people who abuse these substances are needed. It may be that longer term registries are 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 community has made major progress in capitalising on mechanistic knowledge, developing new agents and testing these to improve the biological treatment of MDD. Key

advancements are many agents have a rapid onset of action which will be clinically invaluable in many situations, and they seem tolerable. Many novel and emerging agents also target people with difficult to treat depression, perhaps out of necessity, but there has been a nadir of new interventions for this population over many years and this new evidence will bring hope to that group and their families in particular. Finally, new agents have a wide range of neurochemical targets, consistent with neuroscientific background knowledge of depression, and this can be used as platform for further developments in this therapeutics area, which addresses a priority global need.

List of Table and Figures:

Contributors

SM, RU, EP and AY developed the scope of the piece

SM led the writing of the article

RU and EP contributed to the initial writing of major sections of the article

EP conducted the database searches and EC retrieved article and developed figures

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References

1. Herrman H, Kieling C, McGorry P, Horton R, Sargent J, Patel V. Reducing the global burden of depression: a Lancet–World Psychiatric Association Commission. *The Lancet* 2019; **393**(10189): e42-e3.
2. Depression W. Other common mental disorders: global health estimates. *Geneva: World Health Organization* 2017; **24**.
3. Thapar A, Collishaw S, Pine DS, Thapar AK. Depression in adolescence. *The lancet* 2012; **379**(9820): 1056-67.
4. Pinquart M, Duberstein P. Depression and cancer mortality: a meta-analysis. *Psychological medicine* 2010; **40**(11): 1797-810.
5. Hasler G, Pine D, Kleinbaum D, et al. Depressive symptoms during childhood and adult obesity: the Zurich Cohort Study. *Molecular psychiatry* 2005; **10**(9): 842-50.
6. Nicholson A, Kuper H, Hemingway H. Depression as an aetiologic and prognostic factor in coronary heart disease: a meta-analysis of 6362 events among 146 538 participants in 54 observational studies. *European heart journal* 2006; **27**(23): 2763-74.
7. Price JL, Drevets WC. Neurocircuitry of mood disorders. *Neuropsychopharmacology* 2010; **35**(1): 192-216.
8. Duman RS, Aghajanian GK, Sanacora G, Krystal JH. Synaptic plasticity and depression: new insights from stress and rapid-acting antidepressants. *Nature medicine* 2016; **22**(3): 238-49.
9. BN NA. STAR* D: revising conventional wisdom. *CNS Drugs* 2009; **23**: 627647Schlattner.
10. Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. Lancet. 2018 Apr 7;391(10128):1357-1366.
11. Sanacora G, Treccani G, Popoli M. Towards a glutamate hypothesis of depression: an emerging frontier of neuropsychopharmacology for mood disorders. *Neuropharmacology* 2012; **62**(1): 63-77.
12. Björkholm C, Monteggia LM. BDNF–a key transducer of antidepressant effects. *Neuropharmacology* 2016; **102**: 72-9.
13. Marcantoni WS, Akoumba BS, Wassef M, et al. A systematic review and meta-analysis of the efficacy of intravenous ketamine infusion for treatment resistant depression: January 2009–January 2019. *Journal of Affective Disorders* 2020; **277**: 831-41.
14. Conley AA, Norwood AEQ, Hatvany TC, Griffith JD, Barber KE. Efficacy of ketamine for major depressive episodes at 2, 4, and 6-weeks post-treatment: A meta-analysis. *Psychopharmacology* 2021; **238**(7): 1737-52.

15. Lima TdM, Visacri MB, Aguiar PM. Use of ketamine and esketamine for depression: an overview of systematic reviews with meta-analyses. *European journal of clinical pharmacology* 2021.
16. Popova V, Daly EJ, Trivedi M, et al.: Efficacy and safety of flexibly dosed esketamine nasal spray combined with a newly Initiated oral antidepressant in treatment-resistant depression: a randomized double-blind active-controlled study. Am J Psychiatry. 2019, 176:428-38.
17. Ochs-Ross R, Daly EJ, Zhang Y, et al.: Efficacy and safety of esketamine nasal spray plus an oral antidepressant in elderly patients with treatment-resistant depression-TRANSFORM-3. Am J Geriatr Psychiatry. 2020, 28:121-41.
18. Daly EJ, Trivedi MH, Janik A, et al.: Efficacy of esketamine nasal spray plus oral antidepressant treatment for relapse prevention in patients with treatment-resistant depression: a randomized clinical trial. JAMA Psychiatry. 2019, 76:893-903. 10.1001/jamapsychiatry.2019.1189
19. Sapkota A, Khurshid H, Qureshi IA, et al. Efficacy and Safety of Intranasal Esketamine in Treatment-Resistant Depression in Adults: A Systematic Review. *Cureus* 2021; **13**(8): e17352-e.
20. Wajs E, Aluisio L, Holder R, et al. Esketamine nasal spray plus oral antidepressant in patients with treatment-resistant depression: assessment of long-term safety in a phase 3, open-label study (SUSTAIN-2). *The Journal of clinical psychiatry* 2020; **81**(3): 10773.
21. Capuzzi E, Caldiroli A, Marcatili M, et al. Long-term efficacy of intranasal esketamine in treatment-resistant major depression: A systematic review. *International Journal of Molecular Sciences* 2021; **22**(17): 9338-.
22. Carter B, Strawbridge R, Husain MI, et al. Relative effectiveness of augmentation treatments for treatment-resistant depression: a systematic review and network meta-analysis. *International review of psychiatry (Abingdon, England)* 2020; **32**(5-6): 477-90.
23. Dold M, Bartova L, Kasper S. Treatment Response of Add-On Esketamine Nasal Spray in Resistant Major Depression in Relation to Add-On Second-Generation Antipsychotic Treatment. *The international journal of neuropsychopharmacology* 2020; **23**(7): 440-5.
24. Li X-M, Shi Z-M, Wang P-J, Hu H. Effects of ketamine in electroconvulsive therapy for major depressive disorder: Meta-analysis of randomised controlled trials. *General Psychiatry* 2020; **33**(3): 1-8.
25. Veraart JKE, Smith-Apeldoorn SY, Spaans H-P, Kamphuis J, Schoevers RA. Is ketamine an appropriate alternative to ECT for patients with treatment resistant depression? A systematic review. *Journal of affective disorders* 2021; **281**: 82-9.
26. Dwyer JB, Landeros-Weisenberger A, Johnson JA, et al. Efficacy of Intravenous Ketamine in Adolescent Treatment-Resistant Depression: A Randomized Midazolam-Controlled Trial. *The American journal of psychiatry* 2021; **178**(4): 352-62.
27. George D, Gálvez V, Martin D, et al. Pilot Randomized Controlled Trial of Titrated Subcutaneous Ketamine in Older Patients with Treatment-Resistant Depression. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry* 2017; **25**(11): 1199-209.
28. Ochs-Ross R, Daly EJ, Zhang Y, et al. Efficacy and safety of esketamine nasal spray plus an oral antidepressant in elderly patients with treatment-resistant depression—TRANSFORM-3. *The American Journal of Geriatric Psychiatry* 2020; **28**(2): 121-41.
29. Gupta A, Dhar R, Patadia P, et al. A systematic review of ketamine for the treatment of depression among older adults. *International Psychogeriatrics* 2020; **33**(2): No-Specified.

30. Fedgchin M, Trivedi M, Daly EJ, et al. Efficacy and Safety of Fixed-Dose Esketamine Nasal Spray Combined With a New Oral Antidepressant in Treatment-Resistant Depression: Results of a Randomized, Double-Blind, Active-Controlled Study (TRANSFORM-1). *The international journal of neuropsychopharmacology* 2019; **22**(10): 616-30.
31. Short B, Fong J, Galvez V, Shelker W, Loo CK. Side-effects associated with ketamine use in depression: a systematic review. *The lancet Psychiatry* 2018; **5**(1): 65-78.
32. Jauhar S, Morrison P. Esketamine for treatment resistant depression. British Medical Journal Publishing Group; 2019.
33. Taylor CP, Traynelis SF, Siffert J, Pope LE, Matsumoto RR. Pharmacology of dextromethorphan: Relevance to dextromethorphan/quinidine (Nuedexta®) clinical use. *Pharmacology & therapeutics* 2016; **164**: 170-82.
34. O'gorman C, Anderson A, Jacobson M, Jones A, Tabuteau H. P. 601 AXS-05 (dextromethorphan/bupropion), a novel, oral, investigational agent for major depressive disorder: Results of a randomized, double-blind, active-controlled, multi-center trial (ASCEND). *European Neuropsychopharmacology* 2019; **29**: S410.
35. O'Gorman C, Jones A, Iosifescu DV, Tabuteau H. Efficacy and safety of AXS-05, an oral NMDA receptor antagonist with multimodal activity, in major depressive disorder: results from the GEMINi phase 3, double-blind, placebo-controlled trial. Poster session presented at: ASCP Virtual Meeting; 2020; 2020. p. 29-30.
36. Majeed A, Xiong J, Teopiz KM, et al. Efficacy of dextromethorphan for the treatment of depression: A systematic review of preclinical and clinical trials. *Expert opinion on emerging drugs* 2021; **26**(1): 63-74.
37. De Martin S, Gabbia D, Folli F, et al. REL-1017 (esmethadone) increases circulating BDNF levels in healthy subjects of a phase 1 clinical study. *Frontiers in pharmacology* 2021; **12**: 973.
38. Fava M, Stahl S, Pani L, et al. REL-1017 (esmethadone) as adjunctive treatment in patients with major depressive disorder: a phase 2a randomized double-blind trial. *American Journal of Psychiatry* 2022; **179**(2): 122-31.
39. Razza LB, Moffa AH, Moreno ML, et al. A systematic review and meta-analysis on placebo response to repetitive transcranial magnetic stimulation for depression trials. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 2018; **81**: 105-13.
40. Health O. Repetitive Transcranial Magnetic Stimulation for People With Treatment-Resistant Depression: A Health Technology Assessment. In: [Internet] OHTAS, editor. Ontario health technology assessment series; 2021. p. 1-232.
41. Mutz J, Vipulananthan V, Carter B, Hurlemann R, Fu CHY, Young AH. Comparative efficacy and acceptability of non-surgical brain stimulation for the acute treatment of major depressive episodes in adults: Systematic review and network meta-analysis. *BMJ: British Medical Journal* 2019; **364**.
42. Miuli A, Sepede G, Stigliano G, et al. Hypomanic/manic switch after transcranial magnetic stimulation in mood disorders: A systematic review and meta-analysis. *World journal of psychiatry* 2021; **11**(8): 477-90.
43. Hett D, Marwaha S. Repetitive transcranial magnetic stimulation in the treatment of bipolar disorder. *Therapeutic advances in psychopharmacology* 2020; **10**: 2045125320973790.
44. Chen L, Hudaib A-R, Hoy KE, Fitzgerald PB. Efficacy, efficiency and safety of high-frequency repetitive transcranial magnetic stimulation applied more than once a day in depression: A systematic review. *Journal of Affective Disorders* 2020; **277**: 986-96.

45. Sonmez AI, Camsari DD, Nandakumar AL, et al. Accelerated TMS for Depression: A systematic review and meta-analysis. *Psychiatry Research* 2019; **273**: 770-81.
46. Chu H-T, Cheng C-M, Liang C-S, et al. Efficacy and tolerability of theta-burst stimulation for major depression: A systematic review and meta-analysis. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 2021; **106**.
47. Senova S, Cotovio G, Pascual-Leone A, Oliveira-Maia Albino J, Orcid: http://orcid.org AJAIOhooO-M. Durability of antidepressant response to repetitive transcranial magnetic stimulation: Systematic review and meta-analysis. *Brain Stimulation* 2019; **12**(1): 119-28.
48. Miljevic A, Bailey NW, Herring SE, Fitzgerald PB. Potential predictors of depressive relapse following repetitive Transcranial Magnetic Stimulation: A systematic review. *Journal of Affective Disorders* 2019; **256**: 317-23.
49. Cappon D, den Boer T, Jordan C, Yu W, Metzger E, Pascual-Leone A. Transcranial Magnetic Stimulation (TMS) for Geriatric Depression. *Ageing research reviews* 2021: 101531
50. Lee HJ, Kim SM, Kwon JY. Repetitive transcranial magnetic stimulation treatment for peripartum depression: systematic review & meta-analysis. *BMC pregnancy and childbirth* 2021; **21**(1): 118-.
51. Ganho-Ávila A, Poleszczyk A, Mohamed MMA, et al. Efficacy of rTMS in decreasing postnatal depression symptoms: A systematic review. *Psychiatry Research* 2019; **279**: 315-22.
52. Hett D, Rogers J, Humpston C, Marwaha S. Repetitive Transcranial Magnetic Stimulation (rTMS) for the Treatment of Depression in Adolescence: A Systematic Review. *Journal of affective disorders* 2021; **278**: 460-9.
53. Croarkin PE, Elmaadawi AZ, Aaronson ST, et al. Left prefrontal transcranial magnetic stimulation for treatment-resistant depression in adolescents: a double-blind, randomized, sham-controlled trial. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 2021; **46**(2): 462-9.
54. Suen P, Razza LB, Brunoni AR, et al. Determinants of sham response in tDCS depression trials: A systematic review and meta-analysis. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 2021; **109**: 110261-.
55. Moffa AH, Martin D, Alonzo A, et al. Efficacy and acceptability of transcranial direct current stimulation (tDCS) for major depressive disorder: An individual patient data meta-analysis. *Progress in neuro-psychopharmacology & biological psychiatry* 2020; **99**: 109836-.
56. Berlow Y, Vakili AZ, Carpenter L, Philip N. Transcranial Direct Current Stimulation for Depression and Risk of Treatment Emergent Mania: An Updated Meta-Analysis. *Biological Psychiatry* 2019; **85**(10 Supplement): S339-S.
57. Fang L, Qin Y, Lian B, et al. A systematic review and meta-analysis of deep brain stimulation in treatment-resistant depression. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 2018; **82**: 224-32.
58. Dougherty DD, Rezai AR, Carpenter LL, et al. A randomized sham-controlled trial of deep brain stimulation of the ventral capsule/ventral striatum for chronic treatment-resistant depression. *Biological Psychiatry* 2015; **78**(4): 240-8.
59. Prévot T, Sibille E. Altered GABA-mediated information processing and cognitive dysfunctions in depression and other brain disorders. *Molecular psychiatry* 2021; **26**(1): 151-67.
60. Shaw A, Brealy J, Richardson H, et al. Marked reductions in visual evoked responses but not γ-aminobutyric acid concentrations or γ-band measures in remitted depression. *Biological psychiatry* 2013; **73**(7): 691-8.

61. Kanes S, Colquhoun H, Gunduz-Bruce H, et al. Brexanolone (SAGE-547 injection) in post-partum depression: a randomised controlled trial. *The Lancet* 2017; **390**(10093): 480-9.
62. Meltzer-Brody S, Colquhoun H, Riesenberg R, et al. Brexanolone injection in post-partum depression: two multicentre, double-blind, randomised, placebo-controlled, phase 3 trials. *The Lancet* 2018; **392**(10152): 1058-70.
63. Kumar PS, Sharma A, Andrade C. A pilot, open-label investigation of the efficacy of glucosamine for the treatment of major depression. *Asian Journal of Psychiatry* 2020; **52**: 102113.
64. Wagner-Jauregg T, Wagner W, Vonderbank H. Über die Hemmwirkung einiger Amine auf das Wachstum von Tuberkelbazillen. *The Science of Nature* 1949; **36**(1): 30-.
65. Bai S, Guo W, Feng Y, et al. Efficacy and safety of anti-inflammatory agents for the treatment of major depressive disorder: a systematic review and meta-analysis of randomised controlled trials. *Journal of Neurology, Neurosurgery & Psychiatry* 2020; **91**(1): 21-32.
66. Köhler-Forsberg O, N. Lydholm C, Hjorthøj C, Nordentoft M, Mors O, Benros M. Efficacy of anti-inflammatory treatment on major depressive disorder or depressive symptoms: meta-analysis of clinical trials. *Acta Psychiatrica Scandinavica* 2019; **139**(5): 404-19.
67. Husain MI, Chaudhry IB, Khoso AB, et al. Minocycline and celecoxib as adjunctive treatments for bipolar depression: a multicentre, factorial design randomised controlled trial. *The Lancet Psychiatry* 2020; **7**(6): 515-27.
68. Berk M, Woods RL, Nelson MR, et al. Effect of aspirin vs placebo on the prevention of depression in older people: a randomized clinical trial. *JAMA psychiatry* 2020; **77**(10): 1012-20.
69. Deakin B, Suckling J, Barnes TR, et al. The benefit of minocycline on negative symptoms of schizophrenia in patients with recent-onset psychosis (BeneMin): a randomised, double-blind, placebo-controlled trial. *The lancet psychiatry* 2018; **5**(11): 885-94.
70. Nettis MA. Minocycline in Major Depressive Disorder: And overview with considerations on treatment-resistance and comparisons with other psychiatric disorders. *Brain, Behavior, & Immunity-Health* 2021; **17**: 100335.
71. Andersen KA, Carhart-Harris R, Nutt DJ, Erritzoe D. Therapeutic effects of classic serotonergic psychedelics: A systematic review of modern-era clinical studies. *Acta Psychiatrica Scandinavica* 2021; **143**(2): 101-18.
72. Nutt D. Psychedelic drugs—a new era in psychiatry? *Dialogues in clinical neuroscience* 2022.
73. Carhart-Harris RL. How do psychedelics work? *Current opinion in psychiatry* 2019; **32**(1): 16-21.
74. Daws RE, Timmermann C, Giribaldi B, et al. Increased global integration in the brain after psilocybin therapy for depression. *Nature medicine* 2022; **28**(4): 844-51.
75. Palhano-Fontes F, Barreto D, Onias H, et al. Rapid antidepressant effects of the psychedelic ayahuasca in treatment-resistant depression: a randomized placebo-controlled trial. *Psychological medicine* 2019; **49**(4): 655-63.
76. Sanches RF, de Lima Osório F, Dos Santos RG, et al. Antidepressant effects of a single dose of ayahuasca in patients with recurrent depression: a SPECT study. *Journal of clinical psychopharmacology* 2016; **36**(1): 77-81.
77. Davis AK, Barrett FS, May DG, et al. Effects of psilocybin-assisted therapy on major depressive disorder: a randomized clinical trial. *JAMA psychiatry* 2021; **78**(5): 481-9.

78. Carhart-Harris RL, Bolstridge M, Day C, et al. Psilocybin with psychological support for treatment-resistant depression: six-month follow-up. *Psychopharmacology* 2018; **235**(2): 399-408.
79. Li N-X, Hu Y-R, Chen W-N, Zhang B. Dose effect of psilocybin on primary and secondary depression: a preliminary systematic review and meta-analysis. *Journal of Affective Disorders* 2022; **296**: 26-34.
80. Carhart-Harris R, Giribaldi B, Watts R, et al. Trial of psilocybin versus escitalopram for depression. *New England Journal of Medicine* 2021; **384**(15): 1402-11.
81. 81. Goodwin, G. M. et al. (in press) Single-Dose Psilocybin for a Treatment Resistant Episode of Major Depression
82. Schimmel N, Breeksema JJ, Smith-Apeldoorn SY, Veraart J, van den Brink W, Schoevers RA. Psychedelics for the treatment of depression, anxiety, and existential distress in patients with a terminal illness: a systematic review. *Psychopharmacology* 2021: 1-19.
83. Caldieraro MA, Cassano Marco A, Orcid: http://orcid.org PAOC. Transcranial and systemic photobiomodulation for major depressive disorder: A systematic review of efficacy, tolerability and biological mechanisms. *Journal of Affective Disorders* 2019; **243**: 262-73.
84. Fava M, Dirks B, Freeman MP, et al. A phase 2, randomized, double-blind, placebo-controlled study of adjunctive pimavanserin in patients with major depressive disorder and an inadequate response to therapy (CLARITY). *The Journal of clinical psychiatry* 2019; **80**(6): 481.
85. Soogrim V, Ruberto VL, Murrough J, Jha MK. Spotlight on Pimavanserin Tartrate and Its Therapeutic Potential in the Treatment of Major Depressive Disorder: The Evidence to Date. *Drug Design, Development and Therapy* 2021; **15**: 151.
86. Kambeitz-Ilankovic L, Koutsouleris N, Upthegrove R. The potential of precision psychiatry: what is in reach? *The British Journal of Psychiatry* 2022; **220**(4): 175-8.
87. Moriarty AS, Meader N, Snell KI, et al. Predicting relapse or recurrence of depression: systematic review of prognostic models. *The British Journal of Psychiatry* 2022: 1-11.
88. Browning M, Bilderbeck AC, Dias R, et al. The clinical effectiveness of using a predictive algorithm to guide antidepressant treatment in primary care (PReDicT): an open-label, randomised controlled trial. *Neuropsychopharmacology* 2021; **46**(7): 1307-14.
89. Lewis G, Marston L, Duffy L, et al. Maintenance or discontinuation of antidepressants in primary care. *New England Journal of Medicine* 2021; **385**(14): 1257-67.