Pharmacological Treatments for Anhedonia

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Abstract Anhedonia – the reduced ability to experience or respond to pleasure – is an important symptom domain for many psychiatric disorders. It is particularly relevant to depression and other mood disorders and it is a diagnostic criterion of a major depressive episode. Developing safe and effective pharmacological interventions for anhedonia is a critical public health need. The current chapter will review the state of the field with respect to both the efficacy of currently available pharmacotherapies for anhedonia and the recent clinical research focusing on new brain targets, including the kappa-opioid receptor and the KCNQ2/3 receptors. The evidence for anti-anhedonic effects of ketamine and psychedelic agents will be reviewed, as well.

Keywords Anhedonia · Antidepressant · Depression · KCNQ · Ketamine · Opioid · Psychedelic · Reward

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Anhedonia is defined as: "markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day" (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition [DSM-V]; American Psychiatric Association, 2013). Characterized by a reduced motivation to engage in pleasurable activities or an inability to experience pleasure, anhedonia is a common feature of many psychiatric disorders, including major depressive disorder (MDD), substance use disorders, psychotic disorders, post-traumatic stress disorder (PTSD), and personality disorders (Treadway and Zald 2011). The transdiagnostic nature of anhedonia and its prevalence across a range of psychiatric disorders encourages an understanding of anhedonia as its own psycho-biological process, which may be present alongside diagnosable psychiatric disorders, but has specific neural substrates underlying its pathology (Husain and Roiser 2018; Zhang et al. 2016). It follows, therefore, that pharmacologic treatment targeting anhedonia should consider the unique neurobiological substrates of anhedonia.

Anhedonia is particularly relevant to depressive disorders. Considered a core feature of the disorder, anhedonia is reported by 40–75% of individuals with MDD (Buckner et al. 2008; Pelizza and Ferrari 2009). The presence of anhedonia in association with MDD is clinically important, as anhedonic symptoms are a predictor of poorer treatment response to selective serotonin reuptake inhibitors (SSRIs) and worse functional outcomes, including increased risk of suicide (Spijker et al. 2001; Vrieze et al. 2013; Vinckier et al. 2017; McMakin et al. 2012; Winer et al. 2014; Fawcett et al. 1990). First-line treatments for MDD (e.g., SSRIs) have shown mixed efficacy for the treatment of anhedonia. While a positive treatment response with respect to overall depressive symptoms is generally associated with improved ability to experience pleasure, there are many cases in which anhedonic symptoms persist, even as other mood-related symptoms are restored (Nutt et al. 2007; Whitton et al. 2016). There is, in fact, potential for antidepressants (particularly SSRIs such as citalopram and fluoxetine) to exacerbate levels of anhedonia due to common side effects like emotional blunting, thereby leaving patients with a greater symptomatic burden (McCabe et al. 2010; Price et al. 2009).To improve clinical outcomes, there is a need for anhedonia-specific pharmacological approaches that are able to address these residual symptoms of anhedonia (Cao et al. 2019).

Anhedonia can manifest as deficits in multiple reward-related domains – including motivation, decision making, anticipation, and consummation of reward – each with its own complex pathophysiology (Treadway and Zald 2011). The reward processes involved in anhedonia – reward valuation, motivation, anticipation, and decision making – map to neural circuitry overlapping with the mesocorticolimbic circuit, including the prefrontal cortex (PFC), the anterior cingulate cortex (ACC), and the striatum (Dillon et al. 2014; Keren et al. 2018; Treadway et al. 2012; Wise 1980). The mesocorticolimbic reward circuit, which connects the ventral tegmental area (VTA) and the nucleus accumbens (NAc) and projects onto the PFC, is the primary pathway for processing and modulating reward-seeking behavior (Dunlop and Nemeroff 2007). Normal functioning of reward-related behavior is sustained by the interplay of the striatum and the medial PFC (mPFC) via the dopaminergic transmitter system and restoration of activity in this system may result in anti-

anhedonic effects. Compounds that demonstrate circuit-engagement relating to these pathways could therefore target symptoms of anhedonia by reversing deficits in the underlying biology (Argyropoulos and Nutt 2013). Indeed, this approach is supported by the National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) initiative, which prescribes a transdiagnostic and dimensional focus, based on neurobiological pathways, for psychiatric research, rather than a focus on psychiatric syndromes per se (Dillon et al. 2014; Insel et al. 2010).

In this chapter, we will review potential therapeutic interventions for the treatment of anhedonia in the context of mood disorders, with focus on the clinical pharmacology of interventions, as well as their potential therapeutic efficacy. We will explore clinical trials conducted in adults with mood disorders, in which anhedonia is an endpoint, measured by a standardized anhedonia rating scale such as the Snaith-Hamilton Pleasure Scale (SHAPS) (Snaith et al. 1995). Some clinical trials relating to anhedonia have utilized functional imaging techniques to probe the effects of potential anti-anhedonic pharmacotherapies on the activity within brain regions related to reward processing. We will consider whether evidence supporting the anti-anhedonic effect of a compound is determined by improvement of clinical symptoms specific to anhedonia or by demonstrating circuit-engagement of anhedonia-related brain regions. While pharmacotherapeutics typically target a range of receptors and pathways, we have grouped agents by their primary mechanisms of action for the purpose of this review. Overall, this chapter will present the current state of the field of pharmacologic agents and their putative anti-anhedonic effects.

1 Kappa-Opioid Receptor Antagonists

The mesolimbic circuit, including the ventral striatum (VS, which includes the NAc) and the VTA, is integral in generating motivation and reward-related behaviors. Both the preclinical work from animal models and the clinical imaging studies implicate abnormal dopaminergic neural activity in the pathophysiology of anhedonia (Nestler and Carlezon 2006), so pharmacotherapies that can alleviate this abnormal neural activity in midbrain circuitry may have anti-anhedonic properties. Two compounds, the kappa-opioid receptor (KOR) antagonist JNJ-67953964 (discussed in this section) and the potassium channel modulator ezogabine (discussed below), have demonstrated anti-anhedonic properties in recent clinical trials. In both cases, the reduction in anhedonic symptoms was correlated with changes in VS activity, suggesting that the compounds exert their therapeutic effects by restoring normal function within dopaminergic mesolimbic reward circuitry.

The κ-opioid system is a neuromodulatory system that can influence mesolimbic circuitry activity related to reward and motivation. Antagonism of KORs modulates the balance of neurotransmitter release onto VS and VTA neurons, resulting in improved reward-related functioning and amelioration of anhedonic symptoms and behaviors (Brooks and O'Donnell 2017; Carlezon and Krystal 2016; Tejeda and

Bonci 2019; Tejeda et al. 2017). The therapeutic potential of targeting the κ-opioid system as a novel approach for the treatment of mood and anxiety disorders was tested within the context of the NIMH FAST-FAIL initiative in a study of JNJ-67953964 (Aticaprant), an orally available, high-affinity ($Ki = 0.8 \pm 0.24$ nM, $IC_{50} = 3.0 \pm 4.6$ nM) KOR antagonist with modest activity at mu and delta opioid receptors (Krystal et al. 2018; Margolis et al. 2020; Rorick-Kehn et al. 2014a, b; Zheng et al. 2013). In a double-blinded, randomized controlled trial, participants were administered JNJ-67953964 10 mg/day or a placebo for the 8-week trial duration (Krystal et al. 2020). The participant group included 89 individuals with MDD, bipolar disorder, anxiety disorders, or PTSD, plus some level of anhedonia (SHAPS $\geq$20), who were free of concurrent medication treatment for their primary psychiatric disorder. The primary outcome was change in VS activation, as measured by functional magnetic resonance imaging (fMRI) during a monetary incentive delay (MID) task. Brain activation is estimated during the reward or penalty conditions compared to a neutral condition to produce the contrasts of interest during the task. Researchers also compared baseline and post-treatment scores on mood-related scales, such as SHAPS and the Hamilton Depression Rating Scale (HDRS). Relative to placebo group, those treated with the study drug had statistically significantly greater VS activation during anticipation of both gain and loss (gain: $F(1,86) = 5.58$, $p < 0.01$, Hedges' $g = 0.58$, loss: ($F(1,86) = 11.7$, $p < 0.001$; $g = 1.12$)), as well as a greater reduction in mean SHAPS score relative to baseline scores ($F(1,86) = 3.35$, $p = 0.0345$; $g = 0.44$; baseline 36.4 ± 8.5 (drug group), 33.4 ± 5.9 (placebo group)) that was correlated with the VS activation changes during reward anticipation. Secondary analysis demonstrated baseline VS activation significantly predicted which participants would show a response to treatment. Interestingly, treatment did not seem to improve symptoms of depression (as measured by HDRS scores; mean baseline HDRS 16.3 ± 5.2 (drug group), 14.8 ± 5.9 (placebo group)), although authors note the study participants represented a mixed diagnostic population, and the study was not designed to determine the effects of KOR antagonism on depression.

In a follow-up report on the NIH FAST-FAIL trial described above, investigators performed a secondary analysis of the effects of treatment with the KOR antagonist, compared to placebo, on reward learning, measured using the Probabilistic Reward Task (PRT) (Pizzagalli et al. 2005). Used by several laboratories, the PRT provides a measure of the effect of prior reinforcement on behavior, an adaptation which appears to be modulated by dopamine signaling through the mesocorticolimbic system (Kaiser et al. 2018; Pizzagalli et al. 2008). While the initial report described improved reward learning after treatment with JNJ-67953964 compared to placebo, the secondary analysis determined that the group differences in reward learning following treatment were driven by an increased propensity to select the stimulus previously paired with more frequent rewards, and a higher learning rate in the KOR antagonist group relative to placebo group (Pizzagalli et al. 2020). Interestingly, while the treatment groups differed on learning rate (which, unlike reward sensitivity, has been linked the DA manipulations in prior computational modeling), they

did not differ on reward sensitivity, suggesting a specificity of KOR treatment on discrete aspects of reward dysfunction and anhedonia (Huys et al. 2013).

2 KCNQ Channel Modulators

Preclinical work in rodent social defeat models – a well-validated chronic stress model of depression and anhedonic behaviors – implicates abnormal firing of VTA neurons in the pathophysiology of the stress-induced anhedonic phenotype (Krishnan et al. 2007; Tye et al. 2013). In this preclinical model paradigm, inbred, docile mice are subjugated to repeated agonistic confrontations with a larger, aggressive, dominant male, which can result in the development of maladaptive behaviors in the subjugated mice, alongside pathological neural activity in their dopaminergic circuitry. Some mice, however, do not develop these maladaptive behaviors after exposure to chronic social defeat, and are termed "resilient" to repeated stress. Unlike susceptible mice, resilient mice appear able to restore normal patterns of midbrain neural activity by engaging homeostatic gene expression mechanisms, including upregulation of membrane-bound ion channels (Friedman et al. 2014). In that vein, pharmacotherapies that engage homeostatic pathways to ameliorate pathological dopaminergic hyperactivity may have similarly anti-anhedonic properties.

A promising mechanism to restore normal dopamine neuron firing is by altering membrane excitability through modulation of membrane-bound ion channels (Russo et al. 2012). Voltage-gated potassium channels of the KCNQ (Kv7) family, which pass the muscarinic current (M-current), alter neuronal excitability and are a potential target for anti-anhedonic pharmacotherapies. The KCNQ family of receptors is comprised of five subtypes (KCNQ1-5 or Kv7.1-5), of which subtype KCNQ2/3 (Kv7.2/3) heteromers are highly expressed throughout the brain and are thought to primarily mediate the M-current (Jentsch 2000). In preclinical studies, stress-resilient mice displayed an upregulation of these KCNQ2/3 channels, which increased M-current and led to the restoration of phasic firing of the VTA and, subsequently, absence of anhedonic symptoms. Daily peripheral administration of the selective KCNQ2/3 channel opener ezogabine was able to restore VTA homeostasis in defeated animals, with improvements in anhedonic and pro-depressive behaviors (Friedman et al. 2016). Ezogabine is a first-in-class KCNQ-selective potassium (K+) channel opener approved by the U.S. FDA for the adjunctive treatment of partial-onset seizures in the 600 to 1,200 mg/day range (Brodie et al. 2010). Ezogabine selectively binds to and activates KCNQ transmembrane K+ ion channels, thereby enhancing transmembrane potassium currents mediated by the KCNQ (KCNQ2/3) family of ion channels. These results highlight the importance of KCNQ channels in the pathology of the helpless phenotype, and the translational potential of channel modulators as pharmacotherapeutic agents for anhedonia.

To date, two clinical trials have been conducted demonstrating the effects of ezogabine on anhedonia-related endpoints in individuals with mood disorders.

The first study was a small, single-arm, open-label clinical trial of ezogabine, in which baseline performance and mood scores were compared to post-treatment at the 10-week trial endpoint. The study group included 18 adults with a primary diagnosis of MDD, plus clinically significant symptoms of anhedonia, as operationalized by a score of at least 20 on the SHAPS at baseline (Tan et al. 2020). Participants were administered ezogabine $\leq$900 mg/day over the trial duration, with the primary outcome being treatment-associated changes in connectivity of the brain reward circuitry and reward learning. Resting-state fMRI was used to compute functional connectivity (RSFC) at baseline vs post-treatment, and reward learning was measured (again, at baseline and after treatment) by the PRT (described above). Mood and mental affect was also quantified across the study duration; depression was quantified by the Montgomery-Åsberg Depression Rating Scale (MADRS) and anhedonia by the SHAPS. Reward learning increased with treatment, and participants' symptoms of both depression and anhedonia decreased from baseline to the 10-week treatment endpoint (MADRS: -13.7 ± 9.6, $t_{17} = -6.01$, $p < 0.001$, Cohen's $d = 2.08$, SHAPS -6.06 ± 5.34, $t_{17} = -4.81$, $p < 0.001$, Cohen's $d = 1.00$). The improvement in SHAPS was noted throughout the study as a function of time ($F(5,85) = 11.84$, $p < 0.001$, partial-$\eta^2 = 0.41$), and the difference remained significant after controlling for depression severity (change in MADRS). The improvement in SHAPS scores was associated with reduced connectivity between the ventral caudate (VCa) – an important reward-related region of the ventral striatum – and the mid-cingulate cortex (MCC) ($z = -4.87$, $k = 411$, $p = 0.004$). Treatment-driven improvements in anhedonia that are demonstrated by this study of ezogabine (which activates KCNQ) suggest that KCNQ modulation may affect a striatal-mid-cingulate circuit involved with affective and cognitive processing. Indeed, the MCC is highly connected to the caudate and the midbrain dopaminergic system and is responsive to appetitive and aversive stimuli (Haber and Knutson 2010; Shackman et al. 2011). However, given the open-label nature of this study, as well as its small size, additional work is needed to determine the effect of KCNQ modulation on brain systems that modulate reward processing, and its efficacy for treating anhedonia.

Building on these pilot findings, the authors initiated a two-site, randomized, controlled trial with 45 participants to test the neurocircuit and clinical effects of ezogabine in adults with a primary depressive disorder (MDD or other unipolar depressive disorder), plus elevated anhedonic symptoms (baseline SHAPS $\geq$20) (Costi et al. 2021). The primary outcome of the study was the drug-treated- vs. placebo-treated group differences in bilateral VS activation while anticipating a potential reward during a monetary incentive flanker task (IFT) after 5 weeks of treatment. A version of the monetary incentive delay task (described in the preceding sections), the IFT allows for measurement of neural activity relating to different aspects of reward-based decision making, including cue presentation and receipt of feedback (Stern et al. 2011). Clinical outcomes included baseline to post-treatment reported symptoms of depression and anhedonia measured by MADRS, SHAPS, and the Temporal Experience of Pleasure Scale (TEPS). The ezogabine group, compared to the placebo group, showed greater improvement in clinical symptoms

of depression (MADRS; baseline 28.3 ± 6.1 (ezo) and 26.8 ± 5.1 (placebo), outcome 12.7 ± 8.7 (ezo) and 18.5 ± 10.1 (placebo), $t = -4.04$, df = 213, $p < 0.001$), hedonic capacity (SHAPS; baseline 38.7 ± 8.1 (ezo) and 33.7 ± 6.0 (placebo), outcome 27.5 ± 8.5 (ezo) and 30 ± 10.9 (placebo), ($t = -4.1$, df = 212, $p < 0.001$)), and ability to anticipate pleasure (TEPS). There was trend-level association between treatment and an increased VS response to reward compared to the placebo, but it did not reach significance (estimate = 0.52, SEM = 0.28; $t = 1.85$, df = 38, $p = 0.07$, Cohen's $d = 0.58$). Of note, however, was a positive correlation, only in the ezogabine group, between the change in VS response to reward and change in anticipatory anhedonia (as measured by TEPS). This may suggest that increased VS activity is associated with increased self-reported anticipation of pleasure. The imaging results, together with the observed clinical improvement in anhedonic symptoms, further support the preclinical mechanism proposing that modulating KCNQ channel activity may restore normal functioning of mesolimbic reward-related circuitry.

Treatment with both JNJ-67953964 and ezogabine resulted in improvement of anhedonic symptoms, suggesting that both therapies hold promise as pharmacological interventions in the treatment of anhedonia, and that restoring pathological activation patterns related to reward functioning could be a target for anti-anhedonic pharmacotherapies. The VS and the VTA – as well as their cortical connections – are regions of interest for bettering our understanding of anhedonia and targeting such regions – particularly with respect to dopaminergic reward circuitry – is a potential avenue for future effective pharmacological treatments for anhedonia.

3 Ketamine

Ketamine is a glutamatergic modulator with substantial clinical evidence supporting its efficacy in the treatment of depression and suicidal ideation (Aan Het Rot et al. 2012; Wilkinson et al. 2018; Witt et al. 2020). The antidepressant mechanism of action of ketamine likely involves NMDA-receptor mediated inhibition of inhibitory GABAergic interneurons in the PFC (Zanos and Gould 2018a; Zanos et al. 2018). The resulting temporary elevation in synaptic glutamate leads to increased AMPA receptor activation and subsequent short- and long-term synaptic plasticity via activation of BDNF and the mTOR pathway (Zanos and Gould 2018b). The result of this cascade is a decreased inhibition and increased synaptic plasticity, which may promote therapeutic neural activity of reward circuitry or increase dopaminergic tone in the mesocorticolimbic pathway (Kokkinou et al. 2018; Pulcu et al. 2021). Several clinical studies have examined the potential anti-anhedonic properties of ketamine, which may be separate from its antidepressant and anti-suicidal effects. The clinical studies described below demonstrate acute and chronic effects of ketamine on neural activity in both cortical regions (ACC, orbitofrontal cortex [OFC], hippocampus) and midbrain regions (striatum), that correlate with its anti-anhedonic effects.

In one of the first clinical studies to investigate the anti-anhedonic mechanisms of ketamine, 36 adults with treatment-resistant bipolar depression were recruited for a randomized, double-blind, placebo-controlled, crossover trial (Lally et al. 2014). All participants received both a single intravenous infusion of racemic ketamine (0.5 mg/kg) and a placebo infusion, separated by 2 weeks. The primary outcome of the study was the difference between baseline to post-treatment MADRS scores, with a secondary outcome being the difference in anticipatory anhedonia (measured by SHAPS). Compared to placebo, injection with ketamine resulted in a greater reduction of SHAPS score, as observed by a main effect of the drug after controlling for change in depressive symptoms by entering the total MADRS score minus item 8 as a covariate in the linear mixed model ($F(1,123) = 7.71$, $p = 0.006$). In this model there was no overall main effect of time ($F(9,176) = 1.42$, $p = 0.18$), nor drug-by time interaction ($F(9,219) = 1.49$, $p = 0.15$), but post-hoc analyses demonstrated a significant reduction in SHAPS scores between ketamine and placebo at days 1-, 3-, 7-, and 14 post-treatment. These results suggest that ketamine has specific anti-anhedonic benefits, in addition to more general antidepressant effects, which can occur as soon as 1 day after treatment and last up to 2 weeks. A subset of patients (21 out of 36) also underwent fluorodeoxyglucose positron emission tomography (FDG-PET) to measure brain glucose metabolism 2 h after infusion. In the imaging outcome, reduction in SHAPS score following ketamine infusion was correlated with increased glucose metabolism in the VS. However, post-hoc analyses found this correlation was primarily explained by change in MADRS score, indicating that reduction in depressive symptoms – but not anhedonic symptoms – was associated with changes in VS activity. Whole-brain and subsequent ROI analyses revealed correlations specifically between improved SHAPS scores (corrected for change in MADRS) at 230 min, but not SHAPS scores at 14 days, and clusters in the dorsal anterior cingulate cortex (dACC), and putamen. Overall, this study suggests a mechanism involving the dACC and putamen that is temporarily connected with the anti-anhedonic effects of ketamine, which may be separate from its antidepressant mechanism of action.

In a secondary analysis, the same group studied the anti-anhedonic effects of ketamine in an open-label study of IV ketamine with either adjunctive oral riluzole or placebo (Lally et al. 2015). In this study, 52 adults with unipolar treatment-resistant depression (TRD) received a single IV dose of racemic ketamine (0.5 mg/kg), followed by oral riluzole or placebo for 4 weeks. A rapid reduction in anhedonia (SHAPS) was observed in both groups, beginning 40 min after infusion and lasting up to 3 days. There was no main effect of the adjunct, indicating that riluzole did not provide additional anti-anhedonic effects compared to ketamine, alone. In a subset of patients, (19 out of 52), whole-brain analyses of FDG-PET imaging were performed, revealing a trend-level association between increased VS activity and decreased SHAPS score. After controlling for reduction in MADRS, changes in activity of two regions – the hippocampus and OFC – remained significantly associated with reduced anhedonia at 230 min following treatment. The authors were also able to replicate their previous findings of significant association between increased dACC activity and improvement in SHAPS, when controlled for total change in MADRS.

A recent study by the same group extended these findings, demonstrating that, in patients with TRD, ketamine improved functional connectivity at 2 days post-infusion in a fronto-striatal network composed of PFC, OFC, and perigenual ACC (Mkrtchian et al. 2021). Post-ketamine increases in connectivity were correlated with reduction in SHAPS scores at both 2 and 10 days after infusion. A secondary outcome of the study investigated the effect of inflammation (as measured by plasma C-reactive protein levels) on ketamine-induced changes in brain connectivity. No significant correlations were observed between post-ketamine changes in connectivity and CRP levels in TRD patients.

Building on these findings, a two-part study investigated reward-based activity in the subgenual anterior cingulate cortex (sgACC) in cases vs. healthy controls (HC), and then tested the effect of ketamine administration on sgACC activation (Morris et al. 2020). Research in non-human primates has implicated over-activation of the sgACC in the neuropathology of anhedonia (Alexander et al. 2019). In the first leg of this study, activation was tested for a group of 48 individuals – 28 with MDD (cases) and 20 without (HC) – by the IFT. Compared to HC, individuals with MDD displayed sgACC hyperactivity in response to positively or negatively-valenced feedback (positive, $t(45) = 2.21$, $p = 0.032$; negative, $t(42) = 3.04$, $p = 0.004$). Furthermore, patients with greater anticipatory anhedonia (TEPS) had greater levels of sgACC hyperactivity in response to positive feedback. In the study's second leg, a group of adults with MDD were administered a single infusion of ketamine (0.5 mg/kg). Ketamine treatment improved symptoms of anhedonia and reduced sgACC hyperactivation in response to positive feedback. Together, these findings are consistent with preclinical findings, suggesting that modulation of ACC activity may be an important mechanism for the anti-anhedonic effects of ketamine.

Several recent, retrospective, post-hoc analyses also provide evidence for a specific anti-anhedonic effect of both racemic ketamine and the *S*-enantiomer, esketamine, which displays slightly higher affinity for NMDAR than the racemic form. A secondary analysis of 203 individuals with MDD assessed anhedonia (SHAPS) before and after treatment with four IV infusions of racemic ketamine (0.5–0.75 mg/kg) over the course of 1–2 weeks; findings revealed a reduction in total SHAPS score (controlled for baseline depression severity) following the first infusion, that remained significant until at least 1 week after treatment (SHAPS, baseline 8.82 ± 0.27, post-infusion 6.26 ± 0.39, $F(2, 235) = 31.6$, $p < 0.001$, Cohen's $f = 0.50$) (Rodrigues et al. 2020). The authors also observed improvements in symptoms of depression, anxiety, and suicidal ideation following treatment, which were partially mediated by the reduction of anhedonic severity. A second study collected data from a group of 45 inpatients and outpatients with either uni- or bipolar depression, who were treated with up to six semi-weekly infusions of racemic ketamine (0.5 mg/kg) in order to assess its effects on anhedonia, as measured by the Beck's Depression Inventory (Thomas et al. 2018). Overall, remission of anhedonia with treatment was achieved for ~35% of patients, and baseline anhedonia was found to be correlated with a reduction in symptoms of depression following treatment. Two additional studies of IV esketamine treatment in adults with uni- or bipolar depression also reported an anti-anhedonic effect of the

enantiomer, which was similar in magnitude to that of racemic ketamine (Delfino et al. 2021; Lins-Silva et al. 2021).

Preliminary results from clinical trials demonstrate that ketamine appears to be rapidly efficacious in reducing anhedonia in patients with both uni- and bipolar depression, potentially accounting for some of its observed efficacy in treating MDD, including treatment-resistant forms. Imaging results from patients with mood disorders that received ketamine treatment implicate both the VS and ACC in the anti-anhedonic effects of ketamine. Independent of reductions in depressive symptoms, post-treatment reduction of ACC hyperactivity or increase in VS activity may partially explain ketamine's acute anti-anhedonic effects. Modulating activity in the VS may represent a common mechanism for anti-anhedonic pharmacology, as increases in reward-related VS activity are observed following treatment with both ketamine and KCNQ modulators (or KOR antagonists). Further research will clarify both the efficacy and mechanisms of ketamine, specifically for treating anhedonia.

4 Psychedelics

A developing area of research is a renewed interest in the use of psychedelic compounds for the treatment of depression and other psychiatric disorders. Psilocybin, a serotonergic psychedelic agent and serotonin receptor agonist, acts on the same neurotransmitter system as classical SSRIs. Unlike the classical antidepressants, however, which increase serotonin in the synaptic cleft by inhibiting serotonin transporters, psilocybin acts as a direct agonist on the serotonin 2A (5-HT2A) receptor to elicit psychedelic effects (Carhart-Harris and Nutt 2017). Several studies examining psilocybin for its antidepressive properties additionally noted anti-anhedonic effects.

Given reports of recreational psilocybin having antidepressant effects, Carhart-Harris et al. designed a feasibility study to assess the potential for psilocybin use in the treatment of patients with unipolar TRD (Carhart-Harris et al. 2016). The open-label, non-blinded study with no control group enrolled 12 participants with moderate-to-severe MDD – defined by a HAM-D score >17 – that did not improve after at least 6 weeks of treatment with at least two different classes of antidepressants. Participants were administered two doses of psilocybin: a "test" dose of 10 mg on dosing day 1, then a "high" dose (the treatment dose) of 25 mg a week later. Participants also received several psychotherapy sessions in the form of: a 3–4 h preparatory session, supportive therapy during the two 4–6 h dosing days, as well as integration sessions after dosing and during follow-up. Treatment efficacy was quantified by the change from baseline (pre-dosing) QIDS and SHAPS scores to scores collected 1, 2, 3, and 5 weeks after the treatment dose (25mg), as well as 3 months from treatment dose administration. Scores on both scales showed improvement after treatment, compared to baseline. The most pronounced QIDS score decrease was observed 2 weeks after administration (QIDS, baseline 19.2 ± 2.0, 2 weeks 6.3 ± 4.6, Hedges' $g = 3.2$, $p < 0.002$). Anhedonia, which

was measured by the SHAPS score, significantly decreased from baseline, both 1 week and 3 months after treatment (SHAPS, baseline 7.5 ± 3.7, 1 week 1.4 ± 2.7, Hedges' $g = 1.9$, $p < 0.002$, 3 months 2.8 ± 3.7, Hedges' $g = 1.3$, $p < 0.002$).

Carhart-Harris et al. concluded from their 2016 study that psilocybin was indeed a potential therapeutic intervention for depressive and anhedonic symptoms in their cohort of individuals with TRD. To further this initial inquiry, the original (2016) study plan was modified to follow participants through 6 months after administration of the psilocybin treatment dose (Carhart-Harris et al. 2018). The study group was composed of 20 patients with unipolar, treatment-resistant, moderate-to-severe depression; of this 20 study cohort, most participants ($n = 12$) had also been in the feasibility study. As before participants were administered two doses of open-label psilocybin – a 10 mg test dose followed week later by a 25 mg treatment dose. QIDS-SR-16 scores were significantly decreased from baseline at all post-treatment test points, with the most significant change occurring between baseline and 1 week from treatment. Anhedonia was assessed by the SHAPS at baseline, then 1 week and 3 months after treatment. The average baseline SHAPS score was 6.6 (SD = 4.1) and showed significant improvement with treatment; SHAPS scores were significantly improved from baseline at both post-treatment follow-ups: −4.6 (CI = 95%) 1 week after treatment and −3.3 (CI = 95%) 3 months after treatment. The SHAPS was scored traditionally, using a scale of 0 to 14, unlike in the ezogabine or FAST-MAS trials, where a 0 to 56 scale was used. Although the study population was relatively small, the preliminary study and its 6-month extension found treatment with psilocybin to be well-tolerated and effective for treating anhedonia for duration of up to 3-months. Further research is needed to disambiguate the relative contributions of psychotherapy and psilocybin to the observed therapeutic effects. Though, as the authors note, a certain level psychological support may be necessary to maintain safety during a clinical trial of psychedelics.

Another study of psilocybin in patients with MDD compared the efficacy of treatment with psilocybin to treatment with an SSRI. Researchers at the Centre for Psychedelic Research at Imperial College London compared the depressive symptoms in patients with MDD before and after treatment with either psilocybin or escitalopram. The phase 2, double-blind trial randomly placed 59 participants (out of 1,000 screened) with long-standing, moderate-to-severe MDD into one of two treatment groups to compare treatment efficacies over 6 weeks (Carhart-Harris et al. 2021). On the two "dosing days", which occurred 2 weeks apart, individuals in the psilocybin group ($n = 30$) were administered 25 mg psilocybin; individuals in the escitalopram group ($n = 29$) were also administered psilocybin on dosing days, but were given a "placebo" dose of 1 mg both times. Participants were then given either a placebo (psilocybin group) or escitalopram (escitalopram group) to take daily for 6 weeks. The primary score of treatment efficacy was the difference between the QIDS-SR-16 score at baseline and post-treatment (6-weeks). At baseline, the psilocybin group had an average QIDS-SR-16 score of 14.5, and a change -8.0 ± 1.0 after 6 weeks. The escitalopram group averaged a baseline QIDS-SR-16 score of 16.4, and a change -6.0 ± 1.0 after 6 weeks. Although not a major

consideration in this study, and, as the authors note, the confidence intervals were not corrected for multiple comparisons, the change between baseline and 6-week scores on the SHAPS (0–14 scale) measurement of anhedonia was greater in the psilocybin group (-4.7 ± 0.6), than the escitalopram group (-2.5 ± 0.6), by a difference of -2.2 (-3.8 to -0.6, 95% CI).

5 Conventional Antidepressants

Conventional antidepressants have demonstrated mixed results in the treatment of anhedonia (Nutt et al. 2007). In some cases, conventional antidepressants exacerbate anhedonic symptoms, due to a commonly observed side effect of emotional blunting (Price et al. 2009). Up to 50% of patients taking SSRIs or serotonin-noradrenaline reuptake inhibitors (SNRIs) for MDD report side effects of emotional numbness or blunted affect (Goodwin et al. 2017). Interestingly, some findings suggest that antidepressants with relatively more activity on noradrenergic, dopaminergic, or melatonergic receptors may have superior benefits with respect to the treatment of anhedonia, compared to agents that are primarily serotonergic. For example, tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs) may be relatively better for reducing anhedonia, compared to SSRIs. Data also suggest that dopaminergic agonists such as pramipexole can alter activity in the mesocorticolimbic circuit, with corresponding changes in reward-related behaviors (Pizzagalli et al. 2008; Whitton et al. 2020).

Several clinical studies have provided evidence of an anti-anhedonic effect of the melatonin analog agomelatine (AGO). Agomelatine is a melatonin receptor (MT1 & MT2) agonist and a serotonin receptor (5HT2c & 5HT2b) antagonist. Preclinical studies suggest that both the melatonergic and serotonergic activities contribute to the antidepressant and anxiolytic effects of agomelatine, perhaps by altering circadian rhythms, or by increasing availability of dopamine and norepinephrine (Stahl 2014). Two prospective studies of outpatients with MDD examined the ability of agomelatine to reduce symptoms of anhedonia. In the first study, 257 outpatients were given agomelatine (25–50 mg/day) for 8 weeks (Gargoloff et al. 2016). Significant reductions in anhedonia were observed in the 143 individuals who completed the study, though these results were not corrected for changes in depression scores. Significant reduction began as early as 1 week into treatment, and continued through the end of treatment (SHAPS (0–14 scale), baseline 8.5 vs. 8 weeks 4.1, $p < 0.001$). Similar reductions in QIDS scores were observed, and changes in QIDS and SHAPS were positively correlated. In a larger prospective study, outpatients with MDD were treated with agomelatine (25–50 mg/day) and changes in depressive and anhedonic symptoms were measured after 10–14 weeks (mean time to endpoint 81.7 ± 12.3 days) of agomelatine treatment ($n = 1{,}570$); similar reductions in MADRS and SHAPS scores (MADRS, change -16.5, $p < 0.0001$; SHAPS (change -7.2, $p < 0.0001$) were observed (Vinckier et al. 2017). This study also observed an improvement in psychosocial functioning as measured by the Questionnaire of Social Functioning (QSF). Improvement of anhedonia was the

strongest predictor of improvement in psychosocial functioning, and mediation analysis revealed that reduced anhedonia over time was linked to improvement in depression and recovery of psychosocial functioning. The authors conclude that anhedonia represents an important target in restoring psychosocial functioning in patients treated for MDD, suggesting that a treatment such as agomelatine – which has both antidepressant and anti-anhedonic properties – may be particularly effective in restoring psychosocial functioning in patients with MDD and moderate anhedonia.

Agomelatine has demonstrated comparable efficacy to SSRIs in the treatment of depression, but several studies have shown that it is more effective than oral antidepressants in the treatment of anhedonia (Hickie and Rogers 2011). An open-label, parallel-group pilot study was conducted to compare anti-anhedonic effects in a cohort of 60 adults with MDD, who were randomized to treatment with agomelatine (25–50 mg/day, $n = 27$) or venlafaxine XR (75–150 mg/day, $n = 21$) over 8 weeks (Martinotti et al. 2012). Both compounds demonstrated similar antidepressant efficacy, but the anti-anhedonic efficacy for agomelatine was significantly greater than for VLX (SHAPS (0–14 scale), VLX, baseline 6.4, endpoint 5.1; AGO, 6.5, endpoint 3.4, difference -1.7 $p < 0.01$). Interestingly, the decrease in SHAPS score associated with agomelatine treatment was significant after just 1 week of treatment, suggesting it had a rapid anti-anhedonic effect.

A multi-site, double-blind, randomized head-to-head study between agomelatine and escitalopram (AGO, $n = 164$, 25–50 mg qd; escitalopram (LEX), $n = 160$, 10–20 mg qd) measured antidepressant efficacy, along with emotional side effects, in a population of adults with MDD over the course of 24 weeks (Corruble et al. 2013). The clinical improvements in depression for AGO were statistically significant and non-inferior to LEX (HAMD, AGO, baseline 26.8 $\pm$ 3.1, change at 12 weeks -18.7 ± 6.9 vs. LEX, baseline 26.6 $\pm$ 2.5, change at 12 weeks -18.3 ± 6.8), as well as in percent response (AGO, 82.6% vs. LEX, 81.3%). A subset of patients (AGO, $n = 25$; LEX, $n = 20$) completed the Questionnaire on the Emotional Side-Effects of Antidepressants (OQESA), a self-report that asks the extent to which participants have experienced a series of emotional events. On certain questions related to anhedonia, the AGO group reported greater improvement than the LEX group at 24 weeks ("Things that I cared about before my illness/problem don't seem important to me anymore," AGO = 16%, LEX = 53%; "My emotions lack intensity," AGO = 28%, LEX = 60%). While not a validated metric for anhedonia, the significant difference in response to these questions between the groups may suggest a superior anti-anhedonic effect of AGO over LEX. Together, these two head-to-head studies demonstrate that AGO has comparable antidepressant effects to standard treatments, with the additional and unique effect of improving may also uniquely improve symptoms of anhedonia.

Two studies have also probed potential mechanisms underlying the anti-anhedonic effects of agomelatine. An 8 week, open-label study, including 27 adults with MDD on agomelatine (25–50 mg PO QD), found that increases in peripheral Brain-Derived Neurotrophic Factor (BDNF) were correlated with improvement in symptoms of depression (HAM-D) (Martinotti et al. 2016). Additionally, variation in BDNF levels was more prominent in participants with greater anhedonia at baseline, suggesting that agomelatine may be preferentially efficacious in this

group. Another study measured changes in C-reactive protein (CRP) levels in 30 adult outpatients (12 males, 18 females) with MDD on agomelatine (25–50 mg QD) for 12 weeks (De Berardis et al. 2017). A significant reduction was observed for SHAPS (baseline, 6.6 ± 2.2, endpoint, 3.1 ± 2.0, $p < 0.001$) along with a significant reduction in mean serum CRP levels (baseline, 2.5 ± 0.6 mg/L; week 12, 1.8 ± 0.5 mg/L) in remitters.

Several mechanisms have been proposed for agomelatine's anti-anhedonic properties. Agomelatine can increase both serotonin and dopamine levels through antagonism of 5HT2C receptors, which may result in a reduction of both depressive and anhedonic symptoms (Racagni et al. 2011). Additionally, treatment with agomelatine may increase central BDNF levels leading to hippocampal neurogenesis and an anti-anhedonic effect. The clinical evidence supports both antidepressant and anti-anhedonic effects of agomelatine, though larger RCTs are necessary to clinically confirm agomelatine's anti-anhedonic properties.

Boyer et al. proposed that the different classes of antidepressants (i.e., whether the drug mediated dopaminergic, serotonergic, or noradrenergic activity) might correspond to stronger clinical outcomes for certain clusters of depressive symptoms (Boyer et al. 2000). The authors characterized the "effect profile" of one antidepressant – sertraline – in the treatment of patients with MDD. Sertraline was chosen for its ability in vitro to mediate the activity of both serotonin and dopamine, thereby potentially allowing it to treat a broader range of symptoms than a typical SSRI. Researchers hypothesized that treatment with sertraline would improve both depressive and anhedonic symptoms. To test this hypothesis, this open-label study enrolled 140 participants with MDD and monitored patient response to sertraline (50–150 mg daily) over an 8-week period, in which the primary metric of medication efficacy was HAM-D score across the study duration. Anhedonia was measured using a predefined subscale of the patient-rated symptom checklist (SCL-90) (Derogatis et al. 1973). Both average HAM-D and anhedonia subscale scores significantly improved throughout the treatment course, with improvements in both noted as early as 1 week. The subscale scores for both depression and anhedonia displayed similar reductions over the course of the study, suggesting that improvements in anhedonia may be related to the reduction of overall depressive symptoms. The relationship between anhedonia and decreased dopamine activity, coupled with in vitro findings that sertraline acts on the dopaminergic system, led researchers to conclude that the role of sertraline in the stimulation of dopaminergic activity improved anhedonia. Vortioxetine is a serotonergic antidepressant with multiple other effector neurotransmitter systems, including norepinephrine (NE), dopamine (DA), amino acids, histamine (HA), and cholinergic systems. A pooled analysis of 11, double-blinded RCTs suggested that treatment with vortioxetine was effective in reducing symptoms of anhedonia (McIntyre et al. 2021).

Several head-to-head trials have been conducted between the SNRI venlafaxine and other oral antidepressants in the treatment of anhedonia. In a double-blind RCT, Light et al. reported no significant difference in the reduction of anhedonic symptoms between treatment with venlafaxine and treatment with fluoxetine (Light et al. 2011). Reporting similar results, and as mentioned in the preceding section,

Martinotti et al. demonstrated both venlafaxine and agomelatine were able to reduce symptoms of anhedonia (SHAPS) in patients with depression. In a post-hoc analysis of five RCTs, McIntyre et al. investigated the anti-anhedonic effects of the serotonin and norepinephrine reuptake inhibitor (SNRI) levomilnacipran, using a four-item subscale of the MADRS to measure anhedonic symptoms: 5 [Reduced Appetite], 7 [Lassitude], 8 [Inability to Feel], and 10 [Suicidal Thoughts] (McIntyre et al. 2016). While these studies were not designed to measure the effectiveness of levomilnacipran for anhedonia, specifically, the improvement in the anhedonia symptoms cluster for the treatment group was significantly different than placebo.

Studies of oral antidepressants with the ablity to increase dopaminergic tone – including dopamine and norepinephrine reuptake inhibitors (DNRIs) and TCAs have demonstrated anti-anhedonic effects of these agents. Bupropion is an antidepressant that acts as both a dopamine and norepinephrine reuptake inhibitor. In a 6-week RCT conducted by Tomarken et al., patients treated with bupropion showed a consistent linear decline in anhedonia, whereas the placebo group initially showed improvement, but trended back toward baseline as the 6 weeks progressed, suggesting that the bupropion lead to a more lasting improvement of anhedonia (Tomarken et al. 2004). Amitifadine is a triple reuptake inhibitor, which can inhibit the reuptake of serotonin, norepinephrine, and dopamine (SNDRI). A 6-week, multicenter, randomized, double-blind, parallel, placebo-controlled study evaluated the efficacy and tolerability of amitifadine in 63 patients with MDD (Tran et al. 2012). Treatment with amitifadine improved scores in an anhedonia grouping of MADRS items 1 (apparent sadness), 2 (reported sadness), 6 (concentration difficulties), 7 (lassitude), and 8 (inability to feel). A study by Jouvent et al. compared the anti-anhedonic effects of the monoamine oxidase inhibitor (MAO-I A) moclobemide to the tricyclic antidepressants (TCA) clomipramine (Jouvent et al. 1998). While both antidepressants showed positive efficacy in reducing anhedonia, patients treated with moclobemide seemed to have a greater and faster improvement of anhedonic symptoms within 1 week compared to clomipramine, where effects were not seen until 4 weeks.

6 Conclusion

Anhedonia is a transdiagnostic symptom of reduced capacity to experience pleasure or lack of reactivity to pleasurable stimuli; it has core relevance to mood disorders such as MDD and is also associated with many other psychiatric disorders. Anhedonia in the context of MDD is associated with poor functional outcomes, increased suicide risk and treatment-resistance; first-line antidepressant agents appear to have only limited efficacy against anhedonia. Research indicates that anhedonia can arise through dysregulation with brain systems that control response to reward, with the VTA-NAc dopamine system appearing to be of central importance. In this chapter, we reviewed the data available concerning the efficacy of pharmacotherapy for anhedonia, with a focus on depressive disorders. We began by

summarizing recent experimental medicine approaches to identify pharmacotherapy targeting anhedonia, including work involving the KOR and the KCNQ2/3 systems. We then reviewed data concerning ketamine, psychedelic agents – such as psilocybin – and, finally, conventional antidepressant agents and agomelatine. While the data for the effects of conventional antidepressants on anhedonia are limited, it is likely that agents with activity at systems other than serotonin will be important for the development of future anti-anhedonic agents. In terms of treatment response prediction, baseline reward processing and VS DA function were recently reported to be associated with response to the DA drug pramipexole in adults with depression (Whitton et al. 2020). In a separate recent study, baseline reward sensitivity and fronto-striatal resting-state functional connectivity were related to therapeutic response to atypical antidepressant bupropion in adults with depression who had failed to respond to the SSRI, sertraline (Ang et al. 2020). Both of these studies suggest the potential of reward-related behavioral or brain-based biomarkers to predict response to agents that may preferentially target reward systems (i.e., via their DA- related activity). Work in this area is still in early stages and requires replication. Hopefully, additional research focused on targeting brain systems that mediate reward function will speed the development of safe and effective treatment of anhedonia across psychiatric diagnoses.

Study	Measure	Group	Baseline mean (SD)	Outcome mean (SD)	*N*	Time	Effect size
A randomized proof-of-mechanism trial applying the "fast-fail" approach to evaluating kappa-opioid antagonism as a treatment for anhedonia	HAM-D	JNJ-67953964	16.3 (5.2)	10.8 (4.0)	45	8 weeks	Hedges' $g = 0.44$, $p = 0.03$
		Placebo	14.8 (5.9)	11.1 (3.9)	44	8 weeks	
	SHAPS	JNJ-67953964	36.4 (8.5)	30.8 (3.7)	44	8 weeks	Hedges' $g = 0.09$, $p = >0.10$
		Placebo	33.4 (5.9)	32.4 (3.6)	44	8 weeks	
Effects of the KCNQ channel opener ezogabine on functional connectivity of the ventral striatum and clinical symptoms in patients with major depressive disorder	MADRS	Ezogabine	29.5 (4.9)	−13.7 (9.6), mean change	18	10 weeks	Cohen's $d = 2.08$, $p < 0.001$
						10 weeks	
	SHAPS	Ezogabine	27 to 51	−6.06 (5.34), mean change	18	10 weeks	Cohen's $d = 1.00$, $p < 0.001$
						10 weeks	
Impact of the KCNQ2/3 channel opener ezogabine on reward circuit activity and clinical symptoms in depression: Results from a randomized controlled trial	MADRS	Ezogabine	28.3 (6.1)	12.7 (8.7)	21	5 weeks	Cohen's $d = 0.76$, $p < 0.001$
		Placebo	26.8 (5.1)	18.5 (10.1)	24	5 weeks	
	SHAPS	Ezogabine	38.7 (8.1)	27.5 (8.5)	21	5 weeks	Cohen's $d = 0.64$, $p < 0.001$
		Placebo	33.7 (6.0)	30 (10.9)	24	5 weeks	
Anti-anhedonic effect of ketamine and its neural correlates in treatment-resistant bipolar depression	MADRS	Ketamine	33.92 (5.01)		36	1–14 days	
		Placebo			36	1–14 days	
	SHAPS	Ketamine	37.19 (7.25)		36	1–14 days	
		Placebo			36	1–14 days	
Changes in symptoms of anhedonia in adults with major depressive or bipolar disorder receiving IV ketamine: Results from the Canadian Rapid Treatment center of excellence	QIDS	Ketamine	18.55 (0.33) standard error	13.43 (0.50), (SE)	138	1 week	
					138	1 week	
	SHAPS	Ketamine	8.82 (0.27)standard error	6.26 (0.39), (SE)	139	1 week	Cohen's $f = 0.50$, $p < 0.001$
					139	1 week	

(continued)

(continued)

Study	Measure	Group	Baseline mean (SD)	Outcome mean (SD)	*N*	Time	Effect size
Psilocybin with psychological support for treatment-resistant depression: An open-label feasibility study	QIDS	Psilocybin	19.2 (2.0)	7.4 (4.9)	12	1 week	Hedges' $g = 3.1$, $p = 0.002$
					12	1 week	
	SHAPS	Psilocybin	7.5 (3.7)	1.4 (2.7)	12	1 week	Hedges' $g = 1.9$, $p = 0.002$
					12	1 week	
Trial of psilocybin versus escitalopram for depression	QIDS	Psilocybin	14.5 ± 3.9	−8.0 (1.0), mean change (SE)	30	6 weeks	
		Escitalopram	16.4 ± 4.1	−6.0 (1.0), mean change (SE)	29	6 weeks	
	HAM-D	Psilocybin	19.2 ± 2.3	−10.5 (1.0), mean change (SE)	30	6 weeks	
		Escitalopram	18.4 ± 3.4	−5.1 (1.0), mean change (SE)	29	6 weeks	
	SHAPS	Psilocybin	Not reported	−4.7 (0.6), mean change (SE)	30	6 weeks	
		Escitalopram	Not reported	−2.5 (0.6), mean change (SE)	29	6 weeks	

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