An introduction to Neurostimulation and Interventional Psychiatry

CHAPTER 7

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Introduction

The International Neuromodulation Society defines therapeutic neuromodulation as "the alteration of nerve activity through targeted delivery of a stimulus, such as electrical stimulation or chemical agents, to specific neurological sites in the body." Thus neuromodulation includes electroconvulsive therapy (ECT), Transcranial Magnetic Stimulation (TMS), Magnetic seizure therapy (MST), transcranial Direct Current Stimulation (tDCS) and other forms of transcranial Electrical Stimulation (tES), Deep Brain Stimulation (DBS), vagal nerve stimulation (VNS), focussed ultrasound (FUS) and multiple other treatment approaches under research development. This chapter will focus on the interventional/procedural treatments of ECT, TMS and tDCS, the most widely used forms of therapeutic brain stimulation in neuropsychiatry, as well as ketamine, a relatively new treatment increasingly used worldwide for the treatment of depression.

Electroconvulsive therapy (ECT)

Electroconvulsive therapy (ECT) was first described in 1938[1]. It involves the use of a brief electrical current to stimulate the brain with the aim of inducing a seizure and is typically given while the patient is under general anaesthesia. ECT is thought to exert its therapeutic effects through changes in brain circuit functioning and neurotrophic effects.

Indication and efficacy

ECT is a highly effective acute treatment for severe and/or treatment-resistant depression[2], schizophrenia, mania, catatonic, and neuroleptic malignant syndrome amongst other conditions[3,4], with up to 80% of patients deriving significant clinical benefit. ECT is used worldwide to treat depression, acute psychosis and mania that has not responded adequately to pharmacotherapy. ECT works more rapidly than pharmacotherapy and has also been shown to reduce suicidal ideation[5]. ECT is often listed as second- or third-line intervention in treatment guidelines, indicated where there is a lack of response to two or more trials of pharmacotherapy, an urgent response is required (e.g. due to high suicide risk or inanition), or medication is not tolerated. Acute ECT is commenced two to three times a week, typically for 2-4 weeks, with the number and frequency of treatments tailored to individual response.

The science of ECT has developed rapidly in the last 30 years, with clinical treatment approaches including three common electrode placements (right unilateral (RUL), bifrontal (BF), bifrontotemporal, commonly referred to as bitemporal (BT), see Figure 1), and variations of pulse width (brief pulse, 0.5-2.0 ms) and ultrabrief (<0.5 ms). See Fig 2. Brief pulse RUL, BF and BT ECT have all been shown to be highly effective in treating depression, with bitemporal ECT having the fastest speed of response but also the highest risk of memory impairment[6,7]. Brief pulse BT ECT should be given two rather than three times per week, due to its high efficacy and higher risk of memory impairment. Most research examining outcomes of different ECT treatment approaches has been undertaken in clinical trials in depressed participants and the optimal electrode placement for schizophrenia and mania is not clearly established. The evidence base only supports the use of ultrabrief pulse for the RUL placement[8]. Reducing the pulse width to the ultrabrief range for RUL reduces cognitive risks, but efficacy and speed of response are also reduced.

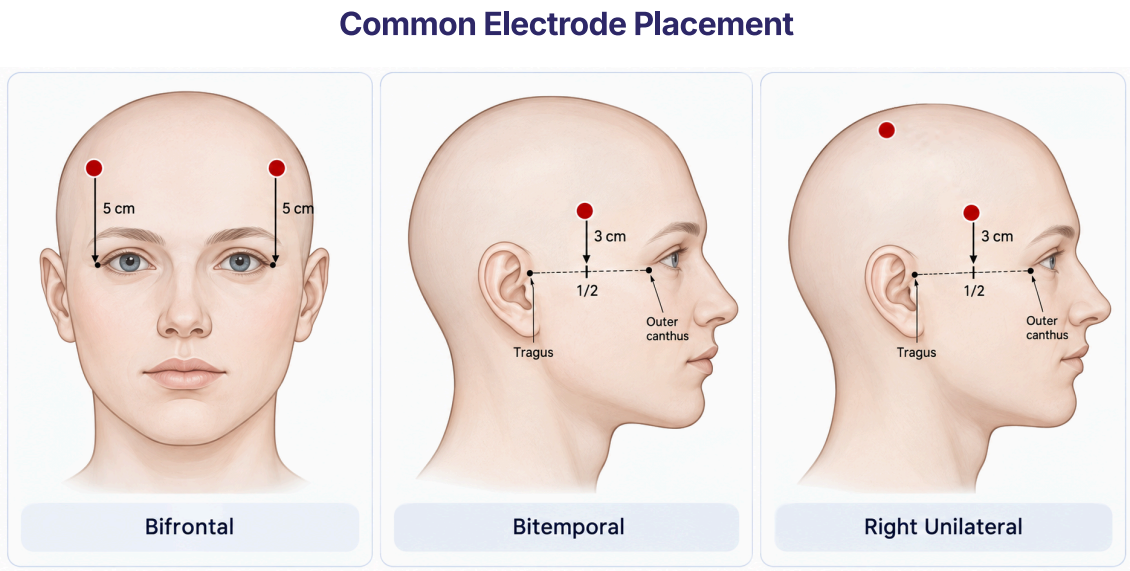


Figure 1- Common electrode placements for ECT treatment. In Bifrontal the leads should be placed 5 cm above the outer canthus of the eyes. Bitemporal – 3 cm above the midpoint of the outer canthus of the eye and the tragus. Right Unilateral – 3 cm above the midpoint of the outer canthus and the tragus as well as 3 cm lateral to the vertex of the head in the direction of the tragus.

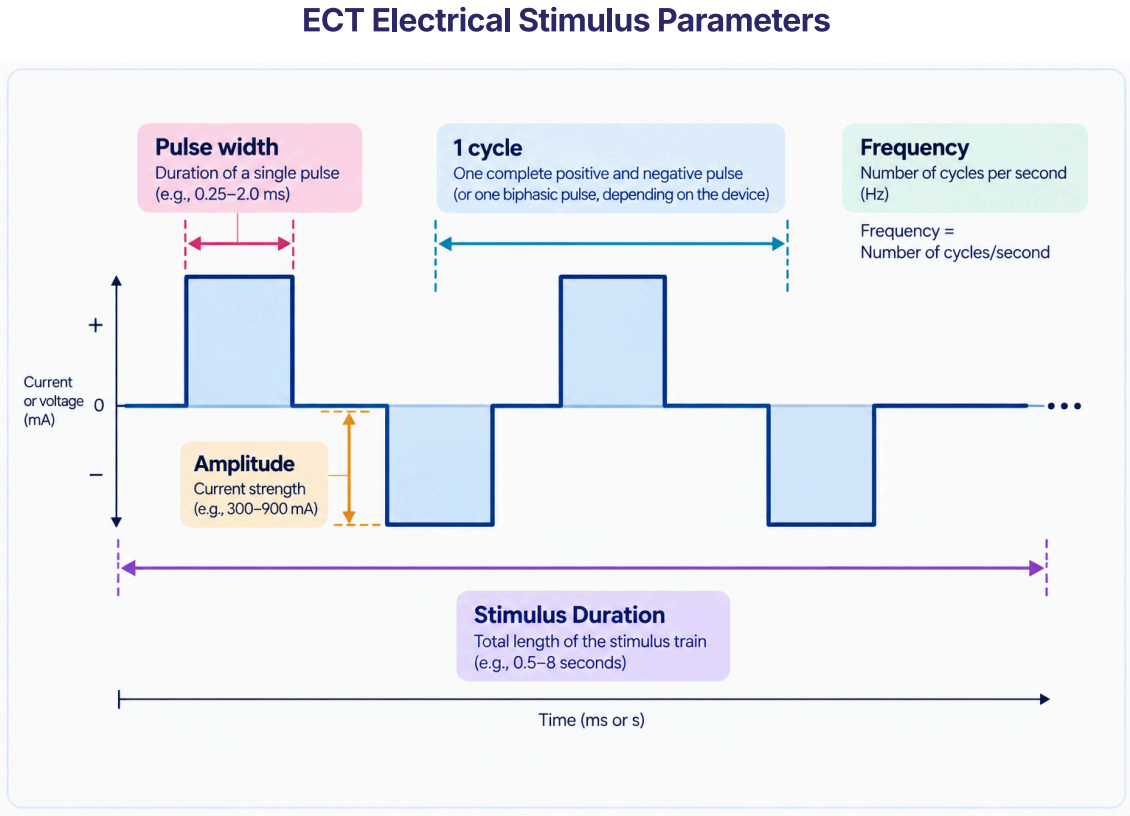


Figure 2 – Electrical stimulus parameters in ECT

Electrical dosing in ECT is important and affects efficacy and cognitive outcomes. In earlier decades a set dose was often used for all patients and all treatments. Clinical trials have shown that adjusting dosage relative to each individual patient's seizure threshold is important for optimising efficacy and cognitive outcomes[7]. This can be done by empirically establishing each individual patient's seizure threshold at the first treatment (starting at a low dosage and increasing until a

seizure is obtained), then individualising dosage in subsequent treatment sessions based on this. Clinical trials have established recommended levels of dosing relative to seizure threshold, for each type of ECT (i.e. combination of electrode placement and pulse width) (See table 1). An alternative approach is to estimate the dosage based on the patient's age ("age-based dosing"), a less accurate approach as age predicts < 25% of a person's seizure threshold.

Table 1: Recommended ECT electrode placement, pulse width and dosage

	Electrode Placement		
Pulse width (ms)	**Bitemporal**	**Bifrontal**	**Right Unilateral**
1.0	1.5 x ST*	1.5 x ST	5-6 x ST
0.5	1.5-2 x ST	2 x ST	6 x ST
0.3	Not recommended	Not recommended	6 x ST

*Dosage is expressed as a multiple of seizure threshold (ST)

Treatment is usually commenced with RUL or BF ECT, then adjusted if there is insufficient improvement after 4-6 brief pulse ECT or 6-8 ultrabrief RUL ECT[9]. ECT may be adjusted by dose, pulse width, and/or electrode placement. There is no single default ECT treatment approach that should be applied to all patients. The ECT treatment approach should be carefully selected for the individual patient, considering clinical priorities and risks, and patient preference, i.e., efficacy and speed of response vs cognitive risks. It is important to consider any history of prior ECT treatment including the type and number of ECT given and treatment outcomes.

Best practice recommends EEG monitoring during the ECT treatment. This usually involves simple 2-channel EEG with electrodes applied to the frontal and mastoid area on both sides of the head. EEG monitoring allows tracking of seizure quality across the ECT course. This can usefully inform on dosing, i.e. a decline in quality indicating likely rise in the patient's seizure threshold, and requirement for increase in the ECT electrical dose. Clinical improvement and cognition should also be tracked over the ECT course, using structured assessment tools, to inform ECT dosing decisions (dose level, number and frequency of treatments).

If there is a clinical response to acute ECT, treatment should not be ceased abruptly, as this results in a high risk of relapse in the following weeks-months[10]. After effective acute treatment, ECT should be gradually tapered (continuation ECT, C ECT), with the speed and duration of tapering individually optimised for each patient[11]. For patients who respond to ECT but have a history of relapse once acute-continuation ECT is ceased, maintenance ECT (M ECT) has been shown to be useful in maintaining benefit[12]. M ECT typically involves one treatment every 2-4 weeks. Patients should be reviewed regularly during acute and maintenance ECT for effectiveness and side effects. Psychotropic medications and therapy have also been shown to be effective in maintaining benefit after acute ECT and should be considered alongside C ECT[13,14].

Safety

Treatment guidelines recommend giving ECT under general anaesthesia. Anaesthesia makes the procedure more comfortable (the ECT stimulus is given while the patient is asleep) and also safer, as a muscle relaxant agent (e.g. rocuronium, suxamethonium) is given to minimise muscle

movement (and hence inadvertent injury) during the generalised seizure. Unmodified ECT (i.e. without anaesthesia) is occasionally given where there is lack of resourcing (e.g. unavailability of anaesthetic staff). This is not considered acceptable in many countries.

ECT should be given under expert psychiatric and anaesthetic specialist medical care. In this context, treatment is safe with complications comparable to minor surgical procedures given under general anaesthetic[15]. Mortality is 1:50,000 treatments. Serious adverse outcomes usually relate to cardiovascular (e.g. arrhythmia) or respiratory (e.g. aspiration) complications and are more common in those with pre-existing medical illness.

Common side effects include headache, muscle aches and pains, nausea, injury to tongue, teeth or soft oral tissues. ECT can cause a manic or hypomanic switch, including in those without bipolar disorder. Other complications include post-ictal agitation or delirium. Patients should have a careful medical examination prior to undergoing ECT, to identify and manage risks. Relative contraindications include recent myocardial infarction, unstable angina, poorly compensated congestive cardiac failure, severe valvular heart disease, cardiac arrhythmias, aortic and intracranial aneurysms, cerebral space-occupying lesions with raised intracranial pressure, recent cerebral haemorrhage and infarction, retinal detachment and glaucoma, and severe pulmonary disease. Raised intracranial pressure was previously considered an absolute contraindication but is now considered a relative contraindication, depending on its severity. Likewise, the presence of a cochlear implant is now considered a relative contraindication, depending on implant device specifics, on which the manufacturer should be consulted. ECT can be safely given in pregnancy with additional precautions (wedge to prevent pressure on inferior vena cavae) and liaison with the obstetrics team.

Cognition

The side effects of most concern for ECT patients are the cognitive risks associated with treatment. These vary widely between individuals and are related to a combination of treatment factors (i.e., electrode placement, pulse width, dose, treatment frequency and number of treatments) and individual factors (i.e., pretreatment cognitive functioning, gender, age). Of these factors, research has demonstrated that the electrode placement and pulse width, as well as an individual's pretreatment cognitive functioning, are most relevant. Specifically, bitemporal ECT compared to other electrode placements and brief pulse width compared to ultrabrief pulse width, are associated with greater cognitive risks. Individuals with higher pretreatment cognitive functioning tend to show the greatest cognitive side effects[16,17].

Of the different cognitive domains, the areas which tend to be most affected are anterograde and retrograde memory and executive functions[18,19]. These cognitive side effects are greatest within the first few weeks following the end of acute treatment, though importantly, tend to either resolve or improve beyond pretreatment cognitive functioning in the months thereafter. Notwithstanding, the cognitive side effect which most persists, is loss of memories for personal and impersonal information acquired prior to the commencement of ECT (i.e., retrograde memory). This memory loss mostly occurs for the period immediately prior to, and during acute ECT treatment. Routine monitoring of cognition prior to and during the ECT course is important, to identify early the onset of these and other cognitive side effects, allowing the ECT treatment to be adjusted to minimise end-of-course cognitive impairment. Brief cognitive screening instruments have been developed and validated for this purpose[20]. Of the different measures, assessment of recovery of orientation after every ECT treatment is most critical, as poorer recovery of orientation after ECT is associated with greater retrograde memory side effects following treatment. With careful implementation, findings

from brief cognitive screening tests can therefore assist in informing treatment decisions which can minimise risk for adverse outcomes (i.e., change in electrode placement, frequency of treatments).

Conclusions

Overall, despite the emergence of newer treatments (other forms of brain stimulation, ketamine, psychedelics) ECT remains an important and effective treatment modality. Further research will hopefully clarify the place of newer treatments in relation to ECT, in the treatment algorithm for depression, schizophrenia and mania.

Transcranial magnetic stimulation (TMS)

Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation technique that uses focussed, high-intensity magnetic fields to induce electrical currents in brain tissue via electromagnetic induction at depths of 2–3 cm[21-23]. When delivered as single pulses, TMS can transiently activate neuronal populations to probe cortical function and determine an individual's sensitivity to TMS, allowing dose titration. They may also be used for functional mapping and determining connectivity through downstream propagation of activity[24].

When pulses are delivered in a series, termed repetitive TMS (rTMS), they can induce longer-lasting changes in neuronal excitability, with effects that may be either inhibitory or excitatory depending on stimulation parameters[25]. A typical course involves three stages: screening for suitability (Table 1), dose determination, and treatment delivery.

	Mnemonic – "SHIMMER
S	Seizures / Epilepsy
H	Headaches
I	Implants (near site of stimulation)
M	Metal in the head
M	MRI-relevant injury (brain injury, stroke, trauma)
E	Eye pathology (e.g., retinal tear)
R	Reactions (prior adverse TMS reaction)

Table 2. *Comprehensive safety screening ought to be performed prior to any TMS to determine contraindication or relative contraindication for rTMS treatment.*

Dosing is achieved by establishing an individual's motor threshold, either the resting motor threshold (RMT) or active motor threshold (AMT). This involves localising the motor cortical representation of a target muscle, most often one controlling a finger (e.g., the first dorsal interosseous) though other muscle groups may be examined (e.g., the hallucis longus or 'big toe lifter'), and adjusting stimulus intensity until a motor response is elicited in at least 50% of trials[26]. Responses may be observed clinically (visible muscle twitch) or measured using electromyography (e.g., ≥50 µV). Treatment is then delivered at a multiple of motor threshold (e.g., 100% - 120%) with the

patient seated comfortably, using a coil (commonly figure-of-eight) positioned over the target cortical region (Figure 2). Parameters vary by indication and whether the goal is to increase or decrease cortical excitability (see Table 3)[27].



Figure 3 - *rTMS treatment session. Patients are placed comfortably in a semi-reclined position, ideally with a neck pillow to improve stability. A TMS coil (figure-of-8 coil depicted) is placed over the treatment site (right-sided stimulation of the dorsolateral prefrontal cortex is shown).*

TMS Frequency	Classification	Typical Effect on Cortical Excitability	Common Clinical/Research Use
1 Hz or Lower	Low-frequency rTMS	Inhibitory	Suppressing hyperactive cortical regions; depression (right DLPFC), tinnitus, stroke rehabilitation
5 Hz	Moderate-frequency rTMS	Excitatory	Alternative antidepressant protocol; cognitive enhancement studies
10 Hz or higher	High-frequency rTMS	Excitatory	Standard FDA/TGA-approved protocol for depression targeting the left DLPFC; Has been used in motor recovery.
iTBS (~50 Hz bursts delivered at 5 Hz for 2 out of every 10 seconds)	Patterned stimulation	Excitatory	Depression treatment targeting left DLPFC; allows for same dose in shorter treatment duration

TMS Frequency	Classification	Typical Effect on Cortical Excitability	Common Clinical/Research Use
cTBS (~50 Hz bursts delivered at 5 Hz continuously)	Patterned stimulation	Inhibitory	Depression treatment targeting right DLPFC; Experimental modulation of cortical activity

Table 3: *Summary of effects of different frequencies of Transcranial Magnetic Stimulation (TMS); DLPFC: dorsolateral prefrontal cortex; iTBS: intermittent theta burst stimulation; cTBS: continuous theta burst stimulation*

Indication and efficacy

rTMS has established efficacy across several neuropsychiatric conditions[28-30]. There is Level A evidence (definite efficacy) for major depressive disorder, neuropathic pain, and aspects of post-stroke motor recovery[31]. In depression, response and remission rates are 58% and 28%, respectively, with higher rates for individuals who complete an adequate treatment course (83% and 62%, respectively)[30] (Table 4). Level B evidence (probable efficacy) supports its use in conditions such as post-traumatic stress disorder, Parkinson's disease (motor symptoms), multiple sclerosis-related spasticity, and chronic post-stroke aphasia[31]. Beyond therapeutic applications, TMS is a powerful neuroscientific tool for establishing causal relationships between brain regions and behaviour, complementing correlational techniques such as functional MRI.

Safety

TMS is generally well tolerated with a favourable side effect profile[32,33]. Common adverse effects include transient scalp discomfort, headache, and fatigue. The loud clicking sound associated with stimulation poses a risk of tinnitus, and hearing protection should be routinely used[34]. A rare but important adverse event is seizure, particularly with excitatory protocols, motor cortex targets, or in individuals with predisposing risk factors (e.g., epilepsy)[35]

TMS characteristic	Prevalence	Sample size (N)
Remission [30]	58%	5010
Response [30]	28%	5010
Headache [36,37]	28-42%	939-950
Scalp discomfort [36]	39%	950
Fatigue [38]	7%	644
Nausea and dizziness [38]	8-11%	584-654
Seizure [39]	<0.001 %	318,560 *treatment sessions*

Table 4. *Efficacy and safety of TMS.*

Conclusions

Overall, since its introduction in 1985, TMS has become an established, safe, and evidence-based technique in interventional psychiatry[40]. Its expanding therapeutic indications and ability to modulate brain function with few side effects (and, importantly, no adverse direct interaction with concomitant medication) position it as a key tool in clinical practice.

Transcranial electrical stimulation (tES)

Transcranial Electrical Stimulation (tES) is the umbrella term for a form of non-invasive brain stimulation (NIBS) which has been investigated as a treatment for mental health disorders in different forms for over 200 years. The most investigated type of TES is transcranial direct current stimulation (tDCS), which was revived and developed into its current modern form from around the year 2000.

tES involves administration of an electrical stimulus below the threshold to stimulate neuronal firing (i.e. subthreshold). The neuromodulatory effects of tES are the result of electrical changes to the neuronal resting state potential, which in turn increases or decreases the probability of neuronal firing in the context of background neuronal activity[41]. Studies have shown that tES produces neuromodulatory aftereffects which persist following stimulation that mimic long-term potentiation (LTP) and long-term depression (LTD) processes[42].

When used to treat mental illness, tDCS is administered using a continuous low-intensity current (usually 1 to 4 milliamperes) via two rubber electrodes (a positively charged anode and negatively charged cathode) placed upon the scalp over cortical brain regions implicated in illness. Treatments are typically between 20 to 30 minutes in duration, and are administered daily for 20 to 40 sessions[43]. tDCS offers distinct advantages relative to other forms of brain stimulation in psychiatry, including its relative low cost, portability, enhanced safety profile, ease of use and capacity for home-based, remotely medically supervised treatment[44].

Indication and efficacy

The primary indication for tDCS is Major Depressive Disorder (MDD). In 2025 the US Food and Drug Administration (FDA) approved a home-based tDCS treatment device for treatment of MDD in persons aged over 18 years who are not considered treatment refractory to medication, i.e., not with treatment resistant depression[45]. This approval was largely based on the results from a large international multicentre randomised controlled trial (RCT)[46], though also considering multiple other large RCTs[43]. This followed similar approvals for other tDCS devices from equivalent regulatory authorities in other jurisdictions, including the United Kingdom, European Union, Australia and Brazil. Current evidence has indicated that for people with MDD receiving tDCS with concurrent medication, that their chance of obtaining treatment response is over 100% higher than staying on ineffective medication alone[47].

tDCS, as well as other forms of tES, including transcranial alternating current stimulation (tACS), have been investigated for multiple other mental health and neurological indications, in particular, schizophrenia, drug and alcohol addiction, cognitive impairment, stroke and Alzheimer's Disease, with results overall showing limited positive effect sizes compared to sham treatment[48]. Given this current state of evidence, tES remains an investigational treatment for other indications until greater evidence bases emerge.

Safety

tES is generally considered safe when administered using modern treatment protocols and devices[49]. The most common temporary side effect which occurs is skin erythema underneath the electrodes which occurs with majority of patients (>90%). Other much rarer side effects include skin burn with improper technique[50], and emergence of hypomania in people with bipolar depression[51].

Conclusions

The ease of administration, low cost, and enhanced accessibility and safety profile of tES relative to other form of brain stimulation makes the treatment uniquely placed relative to other interventional treatments. While the primary indication for tES remains MDD in most jurisdictions, there is considerable scope for its application in other indications with further research development.

Ketamine

Ketamine is a glutamatergic modulator originally developed as an anaesthetic and analgesic and was later found to have rapid antidepressant effects. It is a racemic mixture of R- and S-enantiomers that primarily acts as an N-methyl-D-aspartate (NMDA) receptor antagonist. Its antidepressant effects are thought to arise indirectly via increased glutamate release, activation of AMPA receptors, and downstream neuroplasticity pathways involving brain-derived neurotrophic factor (BDNF) and mammalian target of rapamycin (mTOR) signalling[52] (Figure 4). Ketamine differs from conventional antidepressants by targeting the glutamatergic system rather than monoaminergic pathways.

Ketamine can be administered via intravenous, subcutaneous, intramuscular, or intranasal routes, with differing pharmacokinetic profiles[55]. The relationship between drug pharmacokinetics and antidepressant response is complex and is yet to be fully understood. There is no clear international consensus on the optimal route[56].

Intranasal esketamine (Spravato®) follows a structured dosing protocol, whereas racemic ketamine is administered using an individualised, response-guided dosing regimen (Table 6).

	Esketamine	**Racemic ketamine**
Route	Intranasal	SC/IM/IV*
Regimen	As per protocol	Flexible, response guided
Dose	Start with 56 (28mg if >65 years old) can increase to 84mg.	Start at 0.5mg/kg (subanesthetic dose) and increase based on tolerability and efficacy
Frequency	Commence twice weekly, then taper to weekly and/or fortnightly administration based on efficacy and tolerability.	

***Table 6**. Summary of dosing regimen of esketamine and racemic ketamine *IM= intramuscular, IV= intravenous, kg=kilogram, mg=milligram SC= subcutaneous,*

Indication and efficacy

The primary indication is treatment-resistant depression (TRD), typically defined as failure of at least two adequate antidepressant trials. Both esketamine and racemic ketamine have demonstrated robust efficacy in both short- and long-term treatment[57-60]. Response and remission rates for ketamine and esketamine vary substantially across studies, reflecting differences in the clinical

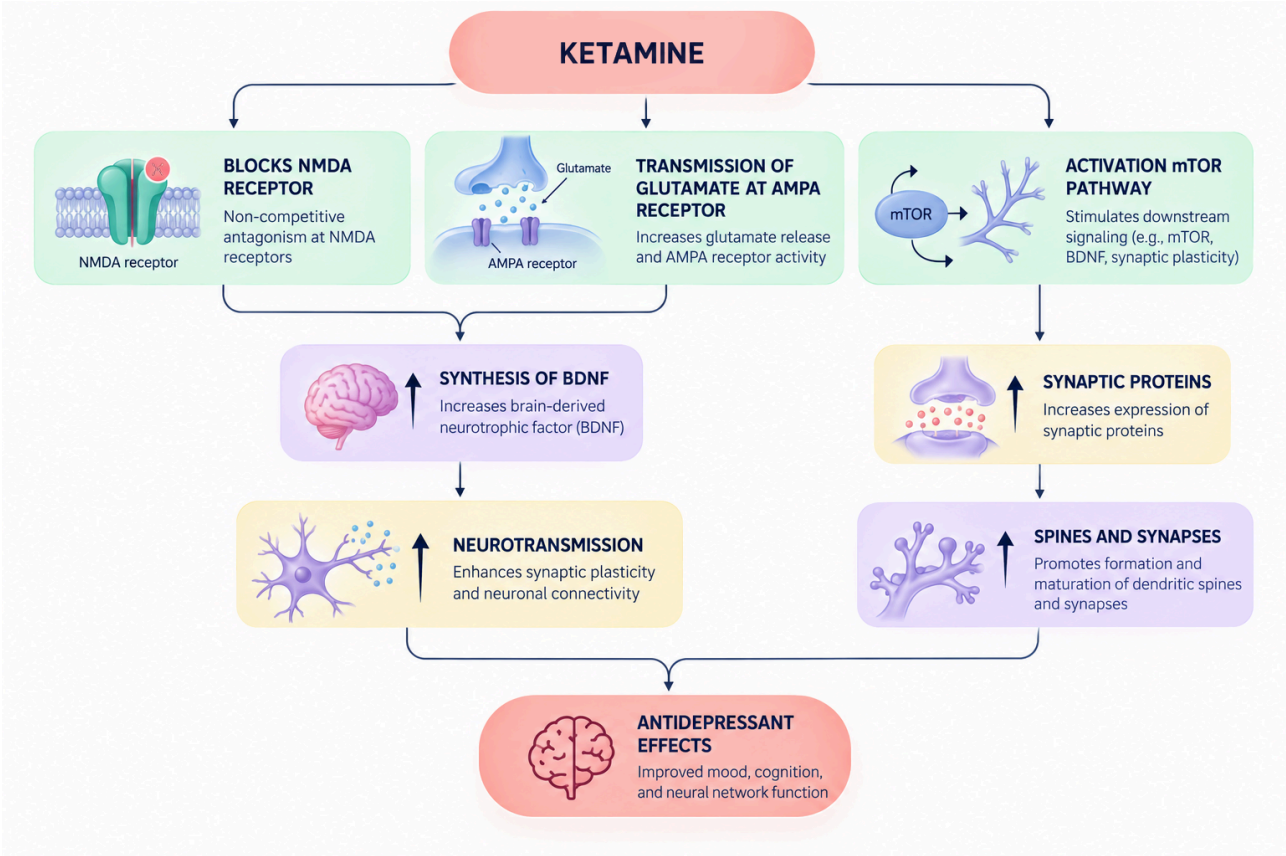


Figure 4. *Proposed mechanism of action of ketamine, based on animal models* [53,54]

population treated and differences in treatment approach (formulation, route of administration, dosing regimen, frequency, comparator and outcome definitions). The pivotal phase 3 placebo-controlled study of intranasal esketamine (Spravato©) tested efficacy in participants who had failed to respond to 2-4 antidepressant medications, with all participants commencing treatment with a new antidepressant medication concurrently with esketamine. Response rates were 69% (esketamine) vs 52 % (placebo) and remission rates 53% (esketamine) vs 31% (placebo)[59]. For racemic ketamine , in the pivotal phase 3 placebo-controlled study ("KADS" trial) which had no upper cut off for prior treatment resistance and included 24% of participants already treated with ECT in the current episode, response rates were 29% (ketamine) vs 4% (placebo), remission rates were 20% (ketamine) vs 2% (placebo)[58]. The study also found that flexible, response-guided dosing was more effective that fixed mg/kg dosing, replicating earlier studies showing individual differences in the mg/kg dosage required for response, supporting the approach of individualised, response-guided dosing[55]. Findings from meta-analyses found both esketamine and ketamine formulations effective compared to placebo/control, with results suggesting higher efficacy with ketamine than esketamine[61,62], e.g. reported relative risks for remission of 3.7 for ketamine and 1.5 for esketamine[61].

A key advantage with ketamine/esketamine treatment is the rapid onset, with symptom improvement often occurring within hours[63]. However, effects may be transient, requiring repeated dosing[63]. Ketamine also shows anti-suicidal effects, which may be partially independent of its antidepressant action[64].

Comparative studies suggest efficacy similar to electroconvulsive therapy (ECT), with recent evidence suggesting potentially faster onset of action[65]. Emerging evidence suggests potential utility in bipolar

depression, although data remain limited. Evidence for other conditions (e.g. OCD, PTSD, substance use disorders) is currently insufficient for routine clinical use[56].

Safety

Ketamine is generally well tolerated in controlled clinical settings. Relative contraindications include significant cardiovascular disease, uncontrolled hypertension, recent cerebrovascular events, psychotic disorders, and pregnancy/breastfeeding)[56,66,67].

Acute adverse effects are dose-related and transient, including dissociation, sedation, dizziness, nausea, and transient hypertension. These typically peak within 40 minutes and resolve within 1–2 hours. Rarely, patients may experience distressing psychotomimetic effects[68].

Long-term risks include urinary tract symptoms (e.g. ketamine-associated cystitis) and potential liver dysfunction. Reported adverse events vary substantially across ketamine studies, reflecting heterogeneity in formulation, route of administration, dosing frequency, study population and methodological aspects of the study. For instance, dissociation has been reported up to 72% of the studies with IV racemic ketamine in TRD compared to 36% in non-intravenous racemic ketamine studies, reflecting differences in peak plasma concentrations[66]. However, a major limitation of the literature is that adverse events are often not assessed systematically and may rely on passive patient reporting, which can lead to underreporting[68]. This highlights the importance of structured and regular monitoring of mental state, blood pressure and cumulative adverse effects, using standardised tools such as the Ketamine Side Effect Tool (KSET)[69].

Conclusions

Ketamine represents a significant development in the treatment of depression, particularly for individuals with TRD. Its rapid onset and including anti-suicidal effects distinguish it from conventional antidepressants. However, its use requires careful patient selection, structured monitoring, and individualised treatment planning. Further research is needed to clarify long-term outcomes and optimise treatment protocols.

Mnemonic – "RAPID"

R	Resistant depression (indication)
A	Acute onset
P	Plasticity mechanism
I	Individualised dosing
D	Duration limited

Psychedelics

'Psychedelic', meaning 'mind-manifesting', describes substances inducing profound mystical-type experiences and perceptual changes. Largely banned in Western countries for 50 years they have re-emerged as potential treatments for certain psychiatric disorders. Divided into three groups: i).

'classic psychedelics' (e.g. lysergic acid diethylamide (LSD), psilocybin) with primary agonism at serotonion-2A (5HT-2A) receptors; ii). empathogens/entactogens, i.e. substances promoting empathy/connectedness (e.g. MDMA), operate via pre-synaptic release of 5HT/other monoamines and, iii): dissociatives (e.g. ketamine, nitrous oxide) are selective antagonists at NMDA receptors.

Mechanisms of action include: i). neuronally, promoting persisting neuroplasticity via rapid synaptogenesis/spinogenesis, ii). at the brain network level, causing acute desynchronisation of neurons in the association cortex and default mode network (DMN), and iii). the subjective level, inducing altered perceptions/states of consciousness. It's been hypothesised that many psychiatric disorders arise from rigid patterns of thinking, with psychedelics allowing RElaxed Beliefs Under pSychedlics (REBUS)[70] facilitating revision of maladaptive beliefs.

Acute subjective effects are highly context dependent, influenced by mind ('set') and 'setting'. The dominant treatment paradigm, psychedelic-assisted therapy (PAT), involves administering drug with psychotherapy or psychological support though the relative contribution of each modality is not established. A typical treatment course utilises two therapists in a 'dyad' and includes: i). preparation sessions building rapport and optimising set and setting, ii). single/multiple dosing sessions, and iii). post-dose integration sessions exploring subjective experiences during dosing, facilitating psychological changes.

Indication and efficacy

Most studies have examined a psychedelic for a specific diagnosis, but psychedelics may be efficacious transdiagnostically. Trial designs pose challenges, e.g. placebo-controlled trials demonstrate functional unblinding impacting interpretation of results.[71]

Post-traumatic stress disorder (PTSD): The most robust evidence in the field relates to MDMA-assisted therapy for PTSD has been examined in two phase III trials using three doses with rapid symptomatic and functional improvement demonstrating medium/large effect sizes[72,73].

Depression: Promising early evidence for psilocybin-assisted therapy in MDD[74] shows large effect sizes and durability as well use in depression/existential distress in individuals with terminal illness[75]. Limited studies have examined treatment-resistant depression (TRD).[76,77]

Other disorders: Current research is examining candidate psychedelics in addiction, anxiety disorders, eating disorders and obsessive compulsive disorder (OCD) as well as non-psychiatric conditions (e.g. traumatic brain injury), headache and pain.

In some jurisdictions (e.g. Australia) clinical treatment with psychedelics is available despite only emerging evidence, with complexities regarding feasibility of models of care, cost, and workforce training.

Safety

Studies have excluded individuals with a personal/family history of schizophrenia/psychosis due to concern about psychotogenic potential, with such risk requiring clarification. Psychedelics have low propensity to induce dependence, overdose and toxicity[78] though monitoring for liking/craving is recommended. Acute alterations in perception/judgment, psychological discomfort and anxiety may occur; longer lasting cognitive/perceptual symptoms, including hallucinogen persisting perception disorder (HPPD), require more data to clarify risk[79].

Conclusions

Psychedelics are powerful mind-altering substances which have re-emerged as a potentially promising treatment paradigm in psychiatry. In most parts of the world, they remain experimental though clinical treatment is available in some jurisdictions despite a limited evidence base. There remain many candidate psychedelics to be researched within distinct diagnostic groups or transdiagnostically. Evidence remains emerging and with a need for more efficacy and safety data especially regarding durability and longer-term safety.

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