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REVIEW ARTICLE

Neurostimulatory and ablative treatment options in major depressive disorder: a systematic review

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Abstract
Introduction Major depressive disorder is one of the most disabling and common diagnoses amongst psychiatric disorders, with a current worldwide prevalence of 5–10% of the general population and up to 20–25% for the lifetime period.
Historical perspective Nowadays, conventional treatment includes psychotherapy and pharmacotherapy; however, more than 60% of the treated patients respond unsatisfactorily, and almost one fifth becomes refractory to these therapies at long-term follow-up.
Nonpharmacological techniques Growing social incapacity and economic burdens make the medical community strive for better therapies, with fewer complications. Various nonpharmacological techniques like electroconvulsive therapy, vagus nerve stimulation, transcranial magnetic stimulation, lesion surgery, and deep brain stimulation have been developed for this purpose.
Discussion We reviewed the literature from the beginning of the twentieth century until July 2009 and described the early clinical effects and main reported complications of these methods.

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Keywords Major depressive disorder · Electroconvulsive therapy · Vagus nerve stimulation · Transcranial magnetic stimulation · Psychosurgery · Deep brain stimulation

Introduction

Major depressive disorder (MDD) is one of the most disabling and common diagnoses throughout psychiatric disorders. It represents a current prevalence of 5% to 10% of the general population according to worldwide large-scale studies, and up to 20% to 25% for the lifetime period [98, 122]. Conventional treatment includes psychotherapy and a wide number of antidepressant drugs; however, over 60% of treated patients responds unsatisfactorily, and almost one fifth becomes refractory to these treatments at long-term follow-up [1, 31, 69, 86, 91]. Therapy failure can lead to a life-threatening situation illustrated by the high number of suicides occurring in up to 15% of individuals [1]. In an attempt to find solutions for this intractable disorder, other more invasive methods have been developed.

Search strategy

All articles and textbooks containing nonpharmacological treatments for MDD, with the exception of psychotherapeutic therapies, were reviewed. The reports were found via Medline search (PubMed) using the following keywords and their combinations: MDD, depression, electroconvulsive therapy (ECT), vagus nerve stimulation (VNS), transcranial magnetic stimulation (TMS), psychosurgery, and deep brain stimulation (DBS). In total, 252 reports and eight textbooks were found describing the use of nondrug-related and nonpsychotherapeutic treatments for depression. Finally, 109 reports were selected for this review; the rest of the articles were excluded due to data repetition or absence of clinical outcome information.

Ablative surgery included lobotomy/leucotomy, orbital and cortical undercutting, cingulectomy (cingulotomy), subcaudate tractotomy, and limbic leucotomy (subcaudate tractotomy with anterior cingulotomy) [17, 18, 55, 62, 78, 104, 120]. Targets for DBS included the subgenual cingulate cortex (Brodmann area 25), nucleus accumbens, ventral caudate/striatum, inferior thalamic peduncle, globus pallidus internus, and the lateral habenula [5, 51, 64, 72, 73, 100, 101]. In this review, we present the early clinical outcome and complications of these different methods.

Historical perspective

Depression is a nosologic entity that has afflicted humankind throughout its existence. The first description of a depressive state was made at the era of Hellenic enlightenment by Hippocrates, derived from one of the four humors, the melancholia. In ancient times, brain surgery was performed to treat mental problems in order to exorcise or appease spirits and ghosts. In 1888, the psychiatrist Gottlieb Burkhardt performed one of the first psychosurgical interventions through cortical excisions with the intention to treat a diagnosed mental illness, schizophrenia in that case. Even though the majority of his patients improved, one of them died, and many others presented serious complications due to the procedure [110]. Consequently, his results were interpreted as careless and unreliable, leaving place to almost 50 years without any related attempt to treat the medically refractory cases. It was not until 1936 that António Egas Moniz, in collaboration with Almeida Lima, brought in modern psychosurgery with apparent better results; these contributions to science led Moniz to receive the Nobel Prize in 1949 [78]. Together, they developed the technique of prefrontal leucotomy to treat severe mental disorders, based on previous studies in primates performed by Fulton and Jacobsen, where frontal lobes were completely removed in two chimpanzees [39]. A few years later, Walter Freeman and James Watts performed lobotomies on numerous cases and popularized this procedure. They even introduced a novel orbital approach with the use of the so-called ice-pick leucotome [37, 38, 118]. Until the 1950s, thousands of lobotomies were carried out around the globe, but the first discordances started to come out when scientific evidence showed no evident benefit of the surgery and, in some cases, even worsening of symptoms. In parallel, ECT was developed and was considered to be a revolutionary technique indicated for acute episodes of severe depression [12]. However, the broad clinical introduction of antipsychotics and antidepressants in the sixties led to a vast decrease in the use of surgical and electroconvulsive procedures for some decades, until the end of the past century.

In recent years, increased interest in psychiatric disorders and the introduction of worldwide accepted, standardized clinical guidelines have made it possible to perform an accurate diagnosis of the illness. Ethical committees have led to stricter diagnostic criteria and a more scientific approach of epidemiological studies. In recent history, newer techniques have also been developed; in the last decades, the novel interventions such as VNS, TMS, and DBS have been added as treating options for MDD. The surgical techniques have become more precise, safer, and more importantly nonlesional.

Electroconvulsive therapy

ECT was introduced in the late 1930s and was very rapidly accepted because of its effectiveness in severe psychiatric disorders. After years of animal experiments by Lucio Bini and Ugo Cerletti, the first patient was successfully treated in 1938 with constant alternant current electrical pulses over 200 V [12, 13, 19, 28]. Even though ECT was originally introduced for schizophrenia solely, this technique was widely used for almost all mental illnesses after a short period of time. Subsequently, when the method gained an ample recognition, the indications, contraindications, and search for proper parameters of stimulation were the subjects of investigation. In the 1950s, ECT and other therapeutic options for the time were eclipsed by the arrival of psychiatric pharmacotherapies; nonetheless, it showed its usefulness again many years later, by being effective in pharmacologically resistant patients [32, 82].

Nowadays, after grand stigmatization for decades, ECT prevails as one of the most effective therapies in the treatment of severe depressive events; it can reach an effect of up to 80% [32]. The repetition of this therapy should only be considered in patients who responded well to previous acute sessions [2]. Unfortunately, the benefit is usually not long lasting [36]. This procedure will probably remain a viable therapeutic option in medically resistant patients. It should never be considered as a first treatment alternative, which remains pharmacotherapy, due to its costs and temporary documented side effects like confusion and retrograde and/or anterograde amnesia [30].

Vagus nerve stimulation

VNS was first introduced as an experimental anticonvulsant procedure in dogs by Jacob Zabara in 1985 [123, 124]. A few years later, Kiffin Penry and Dean treated the first human case with VNS in order to treat epilepsy [87]. After several successful studies of epilepsy conducted in numerous centers, the pioneer case with treatment-refractory depression (TRD) as the indication for VNS was presented by Rush et al. at the end of the 1990s [40, 95]. The rationale was based on the beneficial effects on depressive symptoms in patients who had previously received VNS for seizures, but the exact mechanism of action was not known [26, 43, 49]. Long-term studies have proven the good clinical outcome of VNS for MDD while it is well tolerated; a successful response have been described in half of the patients, with complete remission in one third [40, 95, 96, 102]. Even though its mechanism of action is not completely clarified, immunohistological (in animals) and imaging (in TRD patients) studies have endorsed its clinical effect [81, 85]. It is believed that once the input information from the vagus nerve project into the solitary tract nucleus, it follows an ascending pathway to modulate various structures such as the amygdala, dorsal raphe, locus coeruleus, and the ventromedial prefrontal cortex that produces the effect over mood in patients [85].

Further research is required to elucidate the specific action of VNS, considering the anatomy of the vagus nerve with its projections. Moreover, cost-effectiveness studies are still lacking. Something to keep in mind is that immediately postoperatively and at short-term follow-up, VNS has shown a low effectiveness [76, 102]. However, its beneficial effect at long-term in a substantial amount of patients, together with its low number of unwanted side effects, make this method an attractive treatment for patients suffering from MDD.

Transcranial magnetic stimulation

TMS is an innovative technique and highly appealing to scientists and patients because of its noninvasive nature. TMS directly modulates superficial areas of the brain. It has been recently developed, and several theories about its mechanism of action have been proposed; induction of neurotransmitter release that alters brain physiology and neuronal depolarization seem to be the most important elements, but more data are required to confirm these statements [10, 11, 84]. In recent times, animal and clinical models have been used trying to understand the antidepressant effects of TMS [33, 34, 52–54, 103]; functional imaging has demonstrated specific changes induced by TMS in brain metabolism, perfusion, and interconnections [23].

High-frequency TMS of the left dorsolateral prefrontal cortex has shown effectiveness in almost one third of pharmacotherapy-resistant MDD patients, always with significant differences compared with sham stimulation [6, 83]. Furthermore, differential opposite effects on depressive behavior have been observed when low versus high frequencies were compared [60, 108]. TMS is a safe procedure with no apparent structural damage after usage for several weeks; some of its advantages are its great tolerance in all patients, the lack of cognitive deterioration, or any other unwanted side effects. However, many questions regarding its mechanism of action have to be answered before expanding its use or indications. Another limitation is the duration of the effect, reflected on a worsening of depressive symptoms only 3 weeks after stimulation. This could represent a serious restraint since continuous stimulation is not possible with TMS.

Lesion procedures

Ablative surgery to treat mental illnesses is one of the therapies that has expanded more rapidly and widely as a nonpharmacological therapy. Throughout decades, many targets, approaches, and techniques have been tried, with diverse and sometimes contradictory outcomes. Although the effects on mood gained the attention of medical community, due to the growing prevalence and socioeconomic burden, often no objective measurement of the effects was performed, and probably misdiagnosed patients were included into the studies.

Lobotomy/leucotomy

In 1936, the term psychosurgery was first used in Moniz' prefrontal leucotomy publication in patients with dementia [78]. One year later in 1937, Freeman and Watts introduced a novel approach for the prefrontal leucotomy: the *Freeman–Watts standard lobotomy*, where a 5-cm-long leucotome was introduced through the roof of the orbit in the direction of the sutura coronalis to perform lesions [37]. Leucotomy by that time was accepted by a great part of the medical community as a treatment for patients with several psychiatric disorders. Publications between 1951 and 1972 showed divergent results: improvement was reported in

30% to 100% of patients, but frequently defined only as great/much improvement or moderate/slight improvement [14, 27, 57, 58, 75]. Two studies, however, showed no improvement in the number of discharges from a clinic between patients who underwent leucotomy and the control group [74, 94]. In 1961, a report from the UK by Tooth and Newton showed that from a group of more than 10,000 psychiatric patients with affective disorders, schizophrenia, and other disorders, surgery achieved an improvement of approximately 60%. However, there were many side effects reported such as epilepsy, personality changes, urinary incontinence and, especially, a mortality rate of approximately 4% [114].

Orbital and cortical undercutting

Scoville described in 1949 the supraorbital cortical undercutting of Brodmann areas 9 and 10, the gyrus cinguli, and the orbital surface, based on previous animal experiments that showed these structures play an important role in emotions. It was believed that with this supraorbital approach, discrete lesions could be performed without disturbing the blood supply of surrounding areas. Scoville's first results showed an improvement in all of his affective psychotic patients. Another study with a small number of patients showed an improvement of approximately 85% [104, 105]. In 1955, Knight introduced a variation of Scoville's intervention, the *restricted orbital undercutting*, where he limited the lesion directing his dissection less laterally. Knight based his planning on the circuit of Papez and preferred a restricted resection with the argument that lateral fibers at this level are not of interest for psychiatric disorders; another argument for not going too laterally were the observations that penetrating wounds in the posterolateral lobes resulted in undesirable personality changes. The intervention led to a clear improvement in 69% of patients with depression and various psychiatric conditions [63]. In both Scoville's intervention and its variant described by Knight, the most important side effects included personality changes, epilepsy, and urine incontinence.

Cingulectomy (cingulotomy)

The first description of cingulectomy as a treatment of psychiatric disorders is from Le Beau in 1949. The first cingulectomy reports performed in monkeys resulted in unresponsiveness and placidity when Brodmann's cortical area 24 was aspirated via a fine suction. LeBeau found no improvement of the same treatment in five depressive patients with anxiety and pain but good results in three out of four patients with depression and obsessive neurosis [66]. In 1967, Ballantine described the first stereotactic anterior cingulotomy for psychiatric disorders including depression, after the publication of reports by Foltz and White, who by that time had carried out stereotactic cingulotomies in patients with untreatable pain [9, 35]. The stereotactic neurosurgical technique was applied for the first time in patients by Spiegel and Wycis in 1947. It was a milestone in neurosurgery because specific deep targets could be reached through one burr-hole by using internal cerebral landmarks [109]. Ballantine reported an improvement in 77% of operated patients with comorbid fear and depression. Other studies showed an improvement between 44% and 92% with personality changes, epilepsy, weight gain, and urine incontinence as the most reported side effects [7, 16, 93, 107].

Subcaudate tractotomy

In 1964, Knight described the stereotactic subcaudate tractotomy using radioactive Yttrium implants in order to perform lesions anteroventral to the head of the caudate nucleus in the substantia innominata (SI). The goal was to interrupt the SI fibers that run from the frontal cortex and amygdala to the hypothalamus. Preclinical studies with monkeys had shown that stimulation of Brodmann area 13, an area just under the SI, caused physical phenomena inducing violent emotions. Therefore, Knight reasoned that a lesion in the SI could influence the intensity of emotional responses. From the initial 15 depressive patients whom he operated on, 14 remained therapy-free after surgery [61]. Other studies showed improvement percentages of 59–100%. The most important reported side effects were fatigue, weight gain, and epilepsy in 1–2% of the patients [15, 21, 41, 48, 62, 70, 90, 111].

Limbic leucotomy

In 1973, Kelly and Richardson described the stereotactic limbic leucotomy, which consisted of an anterior cingulotomy in combination with a subcaudate tractotomy. Previous studies involving both areas had shown good results when performed separately. Experimental results had already shown a relation between the autonomous responses and emotions at the level of the limbic system. Intraoperative stimulation was applied to patients in order to evoke physiological responses, which would confirm the exact location of the electrode in the target. Of the first 40 operated patients, five of whom with depression, four showed mild to large improvement of depressive symptoms [55, 56]. Three other studies showed an improvement percentage of 30–78% [57, 79, 97]. The most common reported side effects were drowsiness, weight gain, and memory problems, but also, epilepsy, urine incontinence, and personality changes were described [55–57, 79, 97].

Other procedures

Many other areas and approaches, different from the above-mentioned, have been applied for ablative surgery with the intention to cure mental illnesses; however, only poor results or severe complications were obtained. Some of these procedures include topectomy (also called corticectomy), anterior mesoloviotomy, open frontal leucotomy, and in some cases, multiple targets in the same procedure. The general outcome was reported at short-term follow-up or not mentioned; however, three studies report rehabilitation in 50% of patients or more. Side effects were from moderate to severe, mainly including seizures, personality changes, and postoperative hemorrhage [65, 88, 112, 115].

We summarize some of the most informative and representative outcomes in Table 1.

Deep brain stimulation

Since its successful application for tremor by Benabid et al. in 1987, DBS is applied on a large scale for movement disorders such as Parkinson's disease, tremor, and dystonia. For each indication, different targets and different theories have been developed with the intention to obtain the best clinical results. In DBS (mostly bilateral), electrodes are implanted in specific brain regions where high-frequency stimulation is applied. Its widely appreciated advantages over lesions are its reversibility and adjustability by manipulating the stimulation parameters. Apart from movement disorders, the applications in the last decade have been extended to psychiatric disorders such as Gilles de la Tourette syndrome and obsessive-compulsive disorder (OCD) [42, 68, 106, 117]. In a series of reports performed by Heath et al. between 1979 and 1981, cerebellar stimulation was applied for the treatment of various psychiatric pathologies including intractable depression, schizophrenia, psychiatric conditions secondary to epilepsy, psychotic behavior, and *miscellaneous* psychiatric symptomatology. Concerning the depressive cases, in five out of six patients, the symptomatology decreased significantly at maximum follow-up without medication. However, evaluation of clinical data is difficult to determine due to lack of standardized scales and absence of other updated reports [22, 44–46]. More recently, DBS to treat MDD has followed diverse approaches in order to alleviate depressive symptoms.

In 2005, Mayberg et al. presented the first clinical study of DBS in depression. The hypothesis to stimulate this area was acquired from observations that showed hyperactivity of the subgenual cingulate cortex (Brodmann area 25; Cg25) in chronic depressed patients. It was thought that this area plays a primary role in processes like learning, memory, motivation, and reward—behaviors that change with depression. In this novel study by Mayberg et al., six patients were implanted and stimulated with parameters adjusted to the apparent optimal benefit. After 6 months, in 67% of patients, a reduction of more than 50% on the Hamilton depression rating scale (HDRS) was seen, with a total or partial remission in three patients. Clinically, improvement was referred as an increase in energy, interest, psychomotor speed, and decrease of apathy and anhedonia. In addition, imaging studies showed normalization in the cerebral blood flow of Cg25 and other areas which appear to be related with depression [73].

After this first study, two case reports concerning DBS for depression in different targets were published. In the first report, Jiménez et al. described considerable improvement after DBS of the inferior thalamic peduncle in a 49-year-old woman with a history of recurrent episodes of major depression for over 20 years. After 24 months follow-up of double-blinded stimulation, the score on the HDRS decreased significantly. After a 2-month double-blinded OFF stimulation period, there was an evident worsening of symptomatology with an increase on depressive scales, suggesting that the positive effect was obtained by DBS and not due to a placebo effect [51]. In the second report, Kosel et al. described the case of a 62-year-old woman with treatment refractory MDD with comorbid neuroleptic-induced tardive dyskinesias. DBS of the globus pallidus internus induced an evident drop in the HDRS score after stimulation [64]. Schlaepfer et al. published the positive results of DBS of the nucleus accumbens for depression in three patients, with an immediate effect on depressive ratings. Double-blinded periods with stimulation ON and OFF demonstrated a beneficial outcome only when ON stimulation was applied. Moreover, the positive behavioral changes in these patients were supported by positron emission tomography imaging that correlated symptomatology with an augmentation of metabolism in the nucleus accumbens, amygdala, and dorsolateral and dorsomedial prefrontal cortex, and reduced metabolism in the ventral and ventrolateral medial prefrontal cortex [101]. On the other hand, Aouizerate et al. implanted electrodes in two patients with a history of MDD and OCD. After clinical evaluations, they concluded that the best target for DBS to alleviate OCD symptoms was the ventral caudate, and for the best outcome in depression, the nucleus accumbens was pointed as the best option [3]. In a recent study, Sartorius et al. reported on the case of a 64-year-old woman with history of TRD for over four decades treated with DBS in the lateral habenula. After electrode implantation, the patient presented two relapses, one attributable to initial adjustment of parameters and the second probably due to a traumatism. When the proper functioning of the stimulator was demonstrated, complete remission was achieved for several weeks. After 60 weeks of DBS, the

Table 1 Demographic data from diverse lesion surgical procedures that demonstrates main complications and clinical outcome as stated in original articles

	Author (year)	Number of patients	Outcome	Maximum follow-up	Complications
Leucotomy/lobotomy	Freeman (1937)	3	Good results, patients back to normality	6 weeks	Bleeding in 1 case
	Hutton (1941)	2	Moderate to high improvement	1 month	Bet-wetting for months
	Thorpe (1952)	120	60.8% good result, 20.8% moderate, 18.3% not discharged or death, 6% readmission	24 months	Mortality 3%, seizures 6%, personality changes, impairment of thinking/judgment
	Robin (1958)	43	No improvement in general, only 15 patients showed certain kind of mild benefits	19 years	10 patients died, 9 within the first 6 months postsurgery
	Elithorn (1959)	65	57 patients improved, 10 remained unchanged, and none worsened (according physician), 62 glad, 13 neither glad nor sorry, and 1 regret (self-report elaborated by patients)	Not specified	Not mentioned
	McKissock (1959)	98	54% discharged and working, 23% discharged not working, 17% still admitted, and 5% died	Not specified	Mortality
	Birley (1964)	76	6% symptom-free, 43% much improved, 26% improved, 22% no improved, 1% worse	10 years	1 patient acute confusion, 1 unconscious for hours, 6 severe, and 17 slight personality changes
	McKenzie (1964)	27	22 patients discharged from clinic, no significant difference between surgery and controls	5 years	Not mentioned
	Kelly (1966)	25	9 patients symptom-free, 8 much improved, 7 improved, 1 not improved, 0 worse	6 weeks	Not mentioned
	Post (1968)	33	12 patients with good to moderate improvement, 21 patients with any improvement to poor outcome	3 years	1 death, 40% temporary psychiatric sequelae, 30% permanent changes, 28% disabling effect
	Kelly (1972)	15	3 patients symptom-free, 5 much improved, 3 improved, 4 not improved, 0 worse	18 months	Aggressiveness 3%, minor changes 33%, weight gain 52%, no seizures
	Winter (1972)	3	2 patients with good outcome, 1 fair outcome	Not specified	Not mentioned
	Smith (1977)	17	5 patients symptom-free, 5 much improved, 6 improved, 1 not improved, 0 worse	30 months	3 cases of personality changes (2 disinhibition, 1 apathetic), 2 patients with seizures
Orbital and cortical undercutting	Scoville (1960)	14	24% marked benefit or clinical cure, 28% significant benefit or marked benefit and clinical cure	6.2 years	Mortality 2%, 3 blood clots, 29% one or more seizures, 5% seizures after more than 1 week
	Lewin (1961)	29	12 patients greatly improved, 10 some benefit, 7 showed no improvement	10 years	8 transient incontinence, 3 weight gain, 5 seizures, disinhibition, euphoria
	Knight (1964)	221	91 no symptoms, 64 slight symptoms no treatment, 52 some symptoms requiring treatment, 11 unchanged, 3 deteriorated	Not specified	1.2% mortality, 10% occasional seizures, 5% more than 1 attack despite drugs
	Hirose (1965)	6	1 markedly improved, 3 moderately improved, 2 symptom-free	6.5 years	No mortality
	Scoville (1977)	17	9 cases excellent, 6 good, 2 died	Not specified	4% mortality, 13% seizures, 1% minor stroke, 2% blood clot, 10% personality changes
Cingulectomy/cingulotomy	Whitty (1952)	3	1 temporary improvement, 2 without changes	2 years	1 infection (death), weight gain 12 transient enuresis, 5 incontinences
	Le Beau (1954)	9	3 good results with useful activity postsurgery	3 years	2 deaths, 2 transient hemiparesis, 1 intense anemia
	Lewin (1961)	5	1 greatly improved, 2 some benefit, 2 no improvement at all and died	11 years	1 local osteitis, 1 transient phase of high intracranial pressure
	Cassidy (1965)	15	7 patients good outcome, 6 improved, 2 no changes	3 years	1 suicide and 2 unsuccessful attempts

	Ballantine (1967)	26	75% improved importantly, 15% slightly improved, and 10% no improvement at all	Not specified	3 cases seizures, 4 deaths (1 suicide)
	Brown (1968)	31	87% improved importantly, 4% improved, 4% slight improve, 4% did not improved, 1% worsened	17 years	1 major complication, one third transient urinary incontinence and euphoria
	Bailey (1971)	24	83% very good outcome, 8% remission, 8% marked improvement	Not specified	4 cases infection, 2 seizures
	Whitty (1972)	2	1 patient improved but relapsed, 1 unchanged	12 years	Loss of inhibition and concentration
	Bailey (1973)	71	51 patients with very good outcome, 15 with improvement, 4 slight improvement	1 year	1 death, personality changes, and motivational changes
	Meyer (1973)	22	2 cases very good improvement, 9 marked, 8 moderate, 1 slight, and 2 none	4.5 years	5 confusions, 2 seizures, 2 scalp infections, 1 temporary psychotic increase, 2 suicides
	Bailey (1977)	50	35 patients with very good outcome, 9 improved, 4 slight improvement, 1 unchanged	13 years	0.5% deaths, 7.5% reoperated, 2% suicide
	Teuber (1977)	7	5 patients with full or partial relief	Not specified	Less concentration
	Vikki (1977)	3	2 cases improved slightly, 1 unchanged	Not specified	Indifference and lack of judgment, initiative, and self-criticism
	Martin (1977)	31	14 cases excellent, 7 moderate, 4 slight, 6 none	4 years	2 subdural hematomas, 2 scalp infections
	Corkin (1980)	7	3 marked improvements, and 2 moderate	2 years	2 seizures and transient headache, fever, nausea, vomit, incontinence
	Spangler (1996)	15	30% marked improvement, 40% moderate, 30% slight improvement	Not specified	8 cases unsteady gate, 7 transient urinary retention, 2 seizures, 1 embolism, 2 suicides
	Dougherty (2003)	11	31% of patients with more than 50% of improvement	1 year	Not mentioned
	Richter (2004)	4	No significant improvement	1 year	1 transient urinary incontinence, headache, and nausea
	Ridout (2007)	9	4 recovered, 5 unchanged	14 months	Not mentioned
Subcaudate tractotomy	Knight (1964)	15	8 cases recurred, 5 no symptoms, 3 slight symptoms	Not specified	1 case of seizure
	Ström-Olsen (1971)	75	31 completely recovered, 11 improved slight symptom, 18 improved persistent symptoms, 15 unchanged	2.5 years	3% lasting sequelae, 11% minor symptoms, 86% nonundersirable symptoms, 8 seizures
	Bridges (1973)	24	6 patients symptom-free, 11 much improved, 5 improved, 2 not improved, 0 worse	3 years	1 social disinhibition, 2 lethargy, 1 irritability, 5 patients with at least 1 convulsive episode
	Göktepe (1975)	78	27 patients symptom-free, 26 much improved, 16 improved, 9 not improved, 0 worse	4.5 years	3 suicides, 2 excessive eating, 2 volubility, 2 reduction social standards, 2 extravagance
	Bartlett (1977)	6	0 patients symptom-free, 3 much improved, 2 improved, 1 not improved, 0 worse	1 year	Transient disinhibition, 1 mild aggressive behavior
	Evans (1981)	35	10 patients symptom-free and much improved, 11 improved, 14 not improved, 0 worse	1 year	Not mentioned
	Corn (1984)	6	General improvement of 57% in Hamilton scale	2 weeks	Not mentioned
	Lovett (1989)	15	66% some reduction of symptoms, 33% lower frequency attacks, and 33% less severe symptoms	11 years	4 cases cardiac/respiratory failure, 33% died after 11 years
	Poynton (1995)	16	45% reduction of symptoms at maximum follow-up	6 months	No lasting effect on neuropsychiatric function
	Hodgkiss (1995)	183	63 patients symptom-free and much improved, 53 improved, 57 not improved or worsened	1 year	3% mortality
	Kim (2002)	7	60% improvement at maximum follow-up in Hamilton depression scale	4 years	1 mild transient urinary incontinence
Limbic leucotomy	Kelly (1973)	14	2 patients symptom-free, 2 much improved, 5 improved, 5 not improved, 0 worse	2 years	Short period of confusion and lethargy, transient urinary incontinence, 1 suicide
	Mitchell-Heggs	24	20% patients symptom-free, 6% much improved, 40%	16 months	Confusion, 1 case euphoria, 3 suicides, stereotyped and

Table 1 (continued)

	Author (year)	Number of patients	Outcome	Maximum follow-up	Complications
	(1976)		improved, 20% not improved, 13% worse		perseverative behavior
	Montoya (2002)	6	36% to 50% treatment responders	59 months	2 suicides, 4 seizures, 5 bladder incontinence, 2 memory problems, 1 infection, apathy
	Sachdev (2005)	23	5 patients symptom-free, 11 much improved, 3 improved, 3 not improved, 0 worse	2 years	2 cases epilepsy, 2 weight gain, 8 transient delirium, 6 suicide, 1 death respiratory-related
Other procedures	Pool (1949), topectomy	8	3 cases socially rehabilitated, 1 at home but unstable, 4 improved moderately	Not specified	5 transient urinary retentions, 2 hemiparesis, 7 cases with 2 or more seizures
	Laitinen (1973), anterior mesoloviotomy	5	1 patient symptom-free, 2 improved, 2 unchanged	1 year	1 cases excessive hemorrhage
	Vikki (1977), anterior mesoloviotomy	4	1 patient symptom-free, 2 improved, 1 unchanged	Not specified	3 cases with indifference (lack of judgment, self-criticism, and initiative)
	Peraita (1977), open frontal leucotomy	11	50% significant improvement at maximum follow-up	2 years	Reported "post-leucotomy syndrome"
	Mirsky (1980), multiple targets	17	2 patients symptom-free, 7 much improved, 4 improved, 3 not improved, 1 worse	Not specified	5 seizures, 5 pain syndrome, one third apathy or lethargy, two thirds disinhibition, 6 memory loss

Mortality and seizures remain as serious operative consequences throughout studies with certain regularity. The majority of the rest of side effects related to surgery are mainly referred as temporary

patient remained with an HDRS score of 0 without reported complications or side effects [100].

Nowadays, six main DBS targets of interest remain that have been reported (Table 2). Neuromodulation could be one of the most efficient techniques for this disorder due to the fluctuant behavior of patients and the high co-morbidity that accompanies this condition. Analysis of DBS results of the mentioned targets shows promising responses and evident positive outcomes with minimal side effects. Nevertheless, cost-benefit analysis and good selection of patients are indispensable matters for a successful result.

Discussion

In this review, we have summarized the reports of non-pharmacological therapies for the treatment of MDD, ablative surgery being the first method essayed at the end of the nineteenth century. Even though it was abandoned shortly after its initiation, it was retaken on the 1930s in a systematic manner and applied at various centers with diverse techniques for several decades. Nowadays, these procedures have been abandoned due to the low results with a high complication rate, together with the development of minimally invasive surgery. ECT merged years after psychosurgery as an attractive option at that time to treat many psychiatric conditions without surgical intervention, and showing special aid for severe mood crises, the latter being one of the most important indications even today, with over 80% of improvement if correct inclusion criteria are used. ECT remains a valid intervention even in our days, but with specific indications due to their limitations. Short-lasting effects of this therapy seem to be the most important disadvantage to take into account before its application [32, 116]. At the beginning of the twentieth century, the first case of VNS to treat depression was reported. This therapy has shown since then in various reports, positive outcomes, and good rates of remission for MDD. However, very little about its mechanism of action has been elucidated, and further research is needed to endorse it. During this same time, for over one decade, TMS has been introduced into the psychiatric field, and its therapeutic effect over depression has been examined. Nevertheless, stimulation guidelines and interactions with medications should be better established to avoid relapse of symptoms. Recently, in 2005, the first report of DBS for MDD draws the attention to this well-established method used to treat other conditions for over 20 years. This procedure has demonstrated during this time high rates of remission, low number of side effects, and very few complications related to the surgery.

Several authors have published different outcomes for all of these methods since the first half of the twentieth

Table 2 Reported experience to our days of deep brain stimulation for various targets that demonstrates significant beneficial postsurgery results

	Author (year)	Number of patients	Outcome	Maximum follow-up	Complications
Subgenual cingulate cortex	Mayberg (2005)	6	Striking and sustained remission in 4 of the patients	6 months	Loss of energy and initiative, impaired concentration in 2 patients
	Neimat (2008)	1	Patient reincorporated to full-time job. 68% improvement on Hamilton-D scale	30 months	Not mentioned
	Lozano (2008)	20	60% cases responded to stimulation, 35% patients met criteria for remission	1 year	Infection, perioperative seizures, worsening in mood and irritability, pain in pulse generator site, perioperative headache
Nucleus accumbens	Schlaepher (2008)	3	One case responded significantly, marked differences between ON and OFF states	23 months	No neurological or psychological side effects
Ventral caudate/striatum	Aouizerate (2004)	1	Marked improvement of depression and anxiety until their remission	15 months	Slight attention and executive function tests reduction
	Malone (2009)	15	53.3% of cases responders to stimulation and 40% remission	4 years	Pain at implantation site, hypomania, and probably mixed bipolar state
	Aouizerate (2009)	2	Depression abated (without requirement of antidepressant after surgery in one case)	15 months	Worsening of depressive symptoms in the first 3 months postsurgery
Inferior thalamic peduncle	Jimenez (2005)	1	Complete remission without necessity of medication after surgery	2 years	Not mentioned
Lateral habenula	Sartorius (2009)	1	Complete remission without necessity of medication after surgery	60 weeks	Not mentioned
Globus pallidus internus	Kosel (2007)	1	Significant improvement of 50% on Hamilton-D scale	18 months	HDRS score decreased significantly after 15 and 18 months of stimulation
Cerebellum	Health (1979)	6	83% of patients showed significant improvement without necessity of postsurgery medication	30 months	Major technical problems due to equipment failure

Mild complications are referred with high rates of remission and even abandonment of pharmacotherapy

century. However, in the beginning of the past century, the deficiency of standardized disease criteria, absence of consensus in MDD and TRD definitions, lack of diagnostic instruments, poor follow-up clinimetric evaluations, and high rates of mortality led in many cases to misuse or abuse of these techniques. The poor description of therapy outcomes, complications, and side effects of reports performed in the past complicates an objective evaluation of data in our days. These premises together could have possibly biased the results obtained formerly. The quality of evidence reported in many articles made it very difficult to interpret the results and hardened the data analysis.

On the other hand, the novel developments available nowadays are more ethically justified with better scientific bases, minimally invasive techniques, and more objective evaluation instruments. Innovative procedures as VNS, TMS, and DBS allow physicians to reproduce maximal clinical effects for sustained periods of time that could be adapted to each patient's needs and to combine them with pharmacotherapy [71]. Neuromodulation offers the possibility to adapt parameters to avoid undesired consequences and to obtain the maximum clinical benefit. TMS possesses the advantage over any other therapy by being the least invasive procedure, but still with an unspecific target of action and outcome. ECT is the first line option for acute events in depressive crises. VNS, although proven to be an effective treatment, is not yet a well-established method for MDD. Although in all these therapies the results are promising, their mechanisms of action should be better clarified [84]. Algorithms should be developed to extend these treatments in the most convenient phase of the disorder, allowing also better combination with conventional therapies.

When considering the more invasive treatment options at the present time DBS seems to offer more advantages, fewer complications, and fewer side effects compared with lesions. Moreover, DBS has known more years of careful testing compared with other stimulation methods, its application being supported by larger scientific evidence. Nowadays, lesions should not be considered anymore except if no other alternative is available due to the above-mentioned complications, low rates of success, and irreversibility.

Depression is one of the disorders with the largest comorbidity rate, not only related to other psychiatric conditions but also in association with other illnesses such as Alzheimer and Parkinson disease among others [4, 20, 25, 51, 99]. This premise is another pending aspect that should be kept in mind if real progress is intended for the treatment patients suffering from MDD; in the same way, anxiety-related symptoms should often also be evaluated in order to measure treatment effectiveness.

Future perspective

Novel stimulatory techniques are being developed using minimal invasive techniques. In this respect, DBS seems to be one of the most promising procedures due to its reversibility. DBS also offers the possibility to control the therapeutic effect by simply switching off the stimulation, which is usually not easily possible in other treatments. The main problem of DBS in MDD is at the moment the diversity of potential targets, varying from the cortex to the habenula. One way of solving this problem is to elucidate the mechanism of action of DBS in MDD by using computational and animal models.

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