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Ioannis N. Mavridis, Efstratios-Stylianos Pyrgelis

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REVIEW

Complications of capsulotomy in the treatment of psychiatric illness: A systematic review

Ioannis N. Mavridis,[1] Efstratios-Stylianos Pyrgelis[2]

1. *Department of Neurosurgery, School of Medicine, Democritus University of Thrace, University General Hospital of Alexandroupolis, Alexandroupolis, Greece*
2. *First Department of Neurology, School of Medicine, National and Kapodistrian University of Athens, "Eginition" Hospital, Athens, Greece*

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----------**ABSTRACT**----------

For more than half a century, stereotactic neurosurgical procedures have been available in the treatment of patients with severe, debilitating symptoms of treatment-resistant psychiatric conditions such as obsessive-compulsive disorder (OCD). Such surgical interventions include stimulation and lesioning techniques. Capsulotomy is a lesioning procedure targeting the internal capsule. This systematic review aims to explore the safety profile of capsulotomy in the treatment of severe medically-refractory psychiatric illness, focusing on its complications. Methodologically, a literature search was conducted using the terms "psychiatric", "capsulotomy", and "complications" in the PubMed/Medline database until the end of 2022. The search retrieved 41 articles. Following screening for potential suitability, 39 articles relevant to the topic were further analyzed and finally used for this review. No specific assessment tool for risk of bias was used in this study. The vast majority of capsulotomy data in the literature comes from OCD patients, and the main modalities used for this procedure are radiofrequency (RF) ablation, Gamma Knife radiosurgery (GKRS), and magnetic resonance-guided focused ultrasound (MRgFUS). Postoperative complications are usually transient. These include neurological and psychiatric manifestations, cerebrovascular accidents, thromboembolic events, and infections (respiratory, urinary). Common complications are headache, focal edema, and frontal syndrome. Other complications include ataxia, seizures, urinary incontinence, weight gain, and fatigue. Regarding different techniques, urinary incontinence, sleep disorders, fatigue, and disorientation are frequent but transient complications of RF lesioning. Gamma capsulotomy has a risk of adverse radiation effects, such as radiation necrosis, brain edema, and cyst formation. MRgFUS seems to lack many of the inherent risks associated with more invasive treatment modalities. **Discussion**: Capsulotomy complications, usually transient and self-limited, include neurological and psychiatric manifestations, cerebrovascular accidents, thromboembolic events, and infections. Their occurrence and nature depend on the chosen modality. The principal limitation of this study is the fact that most data come from case reports or case series. As a result, the total number of patients who underwent capsulotomy is limited. Further clinical research is mandatory to improve the safety.

KEYWORDS: Capsulotomy, complications, Gamma Knife, internal capsule, obsessive-compulsive disorder.

Corresponding Author: Ioannis N. Mavridis, Department of Neurosurgery, School of Medicine, Faculty of Health Sciences, Democritus University of Thrace, University General Hospital of Alexandroupolis, Dragana, 68 100 Alexandroupolis, Greece, Email: inmavridis@gmail.com

Introduction

For more than half a century, stereotactic neurosurgical procedures have been available in the treatment of patients with severe, debilitating symptoms of obsessive-compulsive disorder (OCD) refractory to appropriate pharmacological and other treatments.[1] Besides OCD, current literature suggests that specific stereotactic procedures may be efficient and relatively safe in some other treatment-resistant psychiatric conditions such as major depression, pain, and anxiety.[2] Such surgical interventions include stimulation, such as deep brain stimulation (DBS), and lesioning techniques, such as anterior capsulotomy, anterior cingulotomy, subcaudate tractotomy, limbic leucotomy, and central lateral thalamotomy/anterior medial pallidotomy.[3]

Capsulotomy is a lesioning procedure targeting the internal capsule in the treatment of severe refractory psychiatric illness. It can be performed via stereotactic radiofrequency (RF) ablation (thermocapsulotomy, which has been used since the 1950s),[4,5] stereotactic radiosurgery (usually Gamma Knife, gamma capsulotomy),[5-7] and, more recently, magnetic resonance-guided focused ultrasound surgery (MRgFUS), a minimally invasive surgical method of precisely placed focal thermal lesions in the brain.[8] The capsulotomy target involves fibers connecting the mediodorsal thalamus and prefrontal cortex.[5] In RF ablation, which is the cheapest method, a stereotactically (frame-based) inserted electrode creates a thermal lesion at the intended target. In stereotactic radiosurgery (frameless or frame-based), the patient is inserted in the radiosurgical machinery, and focused beams of radiation create a lesion at the predefined target. It is an incisionless procedure. MRgFUS is similar to radiosurgery but uses focused beams of ultrasound instead of radiation and is the less commonly available at the moment.[4-8]

In this systematic review, we aim to explore the safety profile of capsulotomy as a minimally invasive technique to treat severe medically-refractory psychiatric illness, primarily focusing on its complications. The main question to answer is: “Which are the complications of capsulotomy in the treatment of psychiatric illness?”.

Methods

Methodologically, a literature search in the PubMed/Medline database was conducted using the terms “psychiatric”, “capsulotomy”, and “complications” until the end of 2022, which retrieved 41 articles. Following the PRISMA guidelines, the authors screened all articles for potential eligibility using relevance and English language abstracts as inclusion criteria. English language publications, including foreign language publications with abstracts in English, were included in this review. Following screening for potential suitability, 39 articles relevant to the topic (reporting capsulotomy complications) were further analyzed and finally used for this review (**Figure 1**). Two reviewers collected data from each report, and they worked independently. No specific assessment tool for risk of bias was used in this study.

Results

Conditions

Out of 41 publications, 39 that fulfilled the aforementioned inclusion criteria were further analyzed (**Figure 1**). Appropriately selected patients with major treatment-refractory psychiatric disorders can benefit from capsulotomy .[5] Such disorders include severe refractory

OCD,[3-6,9-17] OCD with comorbid schizophrenia,[6] bipolar affective disorder,[18] anorexia nervosa,[9] refractory depression,[2,17,19] chronic and incapacitating anxiety disorders,[2,10,20,21] aggressiveness[22] and intractable chronic pain.[2,10] Remarkably, the vast majority of capsulotomy data in the literature comes from OCD patients (**Table 1**). The main modalities used for capsulotomy are RF ablation, Gamma Knife radiosurgery (GKRS), and, more recently, MRgFUS (**Table 1**). The first two methods have been used for decades, while the third is the newest one.

Complications

Clinical manifestations

Postoperative complications are usually transient and self-limited within a short period. One of the most common complications is frontal syndrome.[11,15] It can manifest as apathy, executive dysfunction, disinhibition, or increased perseverative behavior.[5,9,14] Other usual adverse effects are local edema, often presenting with headache, which responds well to steroids,[3,15,22] ataxia,[22] paraparesis,[22] and seizures, which are usually self-regressive.[3,5,10]Impairment of sphincter control is also common, mainly presenting with urinary incontinence.[3,10,11,19] Other complications include weight gain, somnolence, fatigue,[3,5,10,19] disorientation, bulimia, memory loss, personality changes, lazy behavior, and hypererotism.[23]

Transient postoperative confusion or delirium has also been reported.[3,10] Other psychiatric complications such as hypomania/mania, addiction, suicidal ideation, impaired theory of mind, or negative changes of personality after capsulotomy are relatively rare.[3,14,18-20] Permanent complications such as hemiplegia or cognitive deficits, although reported, are fortunately scarce.[11]

Regarding cerebrovascular accidents following capsulotomy, intracranial hemorrhage is the most common. Infarcts affecting deep structures, e.g., the caudate nucleus, have been reported as well. Thromboembolic complications, such as deep vein thrombosis and air emboli,[3,10,11] as well as cardiac complications, e.g., transient bradycardia with accelerated junctional rhythm,[9] have also been described. Finally, there are several infections that can occur after the procedure, such as pneumonia and urinary tract infections.[3,11] **Table 1** summarizes data regarding indication, sample, method, and complications of capsulotomy in the treatment of psychiatric disorders.

Different modalities

RF lesioning

As seen in **Table 1**, most of the complications mentioned above, as well as multiple adverse events in the same patient, can be observed after RF capsulotomy. The largest series (116 patients) reporting capsulotomy complications so far comes from Liu et al. (2014), who used capsulotomy to treat schizophrenic patients.[23] They reported urinary incontinence, sleep disorder, fatigue, and disorientation as frequent but transient complications. They further noticed long-term complications in their patients that included (in order of frequency) bulimia, memory loss, personality changes, lazy behavior, and hypererotism.[23]

Doshi (2021)[4] reported 107 patients who underwent RF lesioning for movement and psychiatric disorders, including 6 OCD patients who underwent anterior capsulotomy/nucleus accumbens lesioning. All OCD patients were in remission. These authors reported dysarthria, confusion, hemiparesis, dyskinesia, and paresthesia as complications of RF lesioning that occurred in 12 patients (7 were transient), but these were not specific to capsulotomy.[4]

Zhan et al. (2014)[33] studied 53 medically intractable OCD patients who underwent MRI-guided bilateral anterior capsulotomy. Postoperatively, 37.9% were regarded as OCD

symptom-free, 39.5% as clinically improved, and 22.6% experienced no improvement. The authors concluded that bilateral capsulotomy is a precise and relatively safe therapy for refractory OCD, which can improve patients' quality of life and restore their social function. They underlined the necessity of strict inclusion criteria for patients, considering the complications and the irreversibility of this procedure.[33]

Jiménez-Ponce et al. (2011)[34] reported 12 patients with a primary diagnosis of aggressiveness refractory to conventional treatment, who were surgically treated with combined bilateral anterior capsulotomy and cingulotomy. Among them, 5 patients showed either mild or transitory postsurgical complications. According to the authors, the treatment successfully reduced aggressive behavior and improved clinical evaluations.[34]

GKRS

Gupta et al. (2019)[24] have reported the largest series of GKRS capsulotomy for OCD so far. They found mood disturbance as the commonest adverse event, affecting 1/4 of patients. This was followed by worsening in Yale-Brown Obsessive-Compulsive Scale scores and neurological complications, both affecting 7.5% of patients (Table 1).[24]

Gamma capsulotomy has a particular risk of adverse radiation effects, mainly radiation necrosis or brain edema and/or cyst formation. Interestingly, a maximal dose less than 180 Gy is associated with fewer adverse effects [8]. Radionecrotic cysts have been reported in 5% of patients at long-term follow-up.[8] Kasabkojian et al. (2021)[25] underlined that GKRS capsulotomy complications can develop years after treatment, especially in cases of very high radiation doses. They also noted the consequences of severing more fibers of the anterior frontal region than intended and the importance of careful clinical and imaging follow-up.[25]

Miguel et al. (2019)[1] reported frontal lobe edema and formation of delayed radionecrotic cysts as possible complications of GKRS capsulotomy for OCD. These adverse events, however, have become less common with modern radiation dose and targeting strategies. According to these authors, GKRS capsulotomy, and particularly its modern variant, i.e., gamma ventral capsulotomy, appears as a reliable treatment option for selected cases of otherwise highly refractory OCD.[1] Moreover, Batistuzzo et al. (2015) reported a double-blind, randomized controlled trial of GKRS ventral capsulotomy in 16 refractory OCD patients with no decline in cognitive or motor functioning at one-year follow-up.[26]

Remarkably, we should note here that GKRS capsulotomy may be a viable option in patients with treatment-refractory Tourette syndrome with comorbid OCD,[35] as well as for other OCD-related disorders such as skin-picking disorder.[36]

MRgFUS

Mild and transient headache and vestibular symptoms have been reported following MRgFUS[27] (**Table 1**). Kumar et al. (2019)[28] reported a decision analytical model comparing MRgFUS to RF capsulotomy for OCD. Analyzing published data, they mentioned that complications occurred in 16.2% of RF cases. In 1.4% of cases, complications were considered acute/perioperative and incurred additional hospitalization costs. The adverse events, including neurological and neurobehavioral changes, did not incur further costs in the rest 14.8% of cases, although they impacted utility. Compared to RF capsulotomy, MRgFUS appeared more cost-effective. They concluded that MRgFUS lacks many of the inherent risks associated with more invasive treatment modalities for OCD.[28] According to other authors, MRgFUS has the advantages of less invasiveness and a real-time monitored procedure, and this modality is now growing to attempt potential applications to various brain disorders.[37]

Discussion

Anterior capsulotomy is a generally safe, well-tolerated, and effective therapy for OCD.[38] The capsulotomy's surgical target includes the unilateral[5] or bilateral anterior limb of the internal capsule (ALIC),[5,9,11,18-21,27,31] occasionally combined with supragenual cingulotomy.[22] GKRS capsulotomy has been performed for over 40 years in the treatment of refractory OCD. Long-term clinical response data and adverse outcomes from earlier empiric treatment parameters have resulted in shifting the target from its initial location within the midpoint of ALIC to its most ventral portion as well as the ventral striatum,[7] where the nucleus accumbens belongs.[39-41]

Remarkably, many of the early GKRS capsulotomy studies were complicated by clinically relevant radiation-induced adverse effects.[7] More recent GKRS capsulotomy studies have demonstrated strong efficacy with diminished adverse effects with well-placed lesions created at lower radiation doses. Advances in neuroimaging technology, such as diffusion tensor imaging-based fiber tracking, may provide further insight into precisely targeting the ventral capsule/striatum, based on patient-specific variations in white matter connectivity.[7]

Pepper et al. (2015)[42] reviewed the published literature and compared the outcome of ALIC capsulotomy and DBS of the ventral capsule/ventral striatum and nucleus accumbens in OCD. Remarkably, they found no difference in complication rates.[42] Pepper et al. (2019) also reviewed the effectiveness and safety profile of anterior capsulotomy for OCD and found a low rate of serious complications.[38] More recently, Chang et al. (2021)[8] reviewed ablative surgical techniques for OCD, including capsulotomy, and their complications [8]. They found that adverse events following capsulotomy have been reported as transient/mild in 56.2% of patients and as permanent/serious in 21.4% of patients. These complications included apathy, incontinence, seizures, and executive dysfunction; these were also related to a very high radiation dose, multiple procedures, and larger targets. The authors importantly noticed that advancements in the capsulotomy procedure have significantly decreased its adverse events.[8]

Capsulotomy is a type of stereotactic psychiatric surgery that can be an effective and relatively safe treatment option when carried out by a specialized multidisciplinary team, aiming to treat carefully selected patients with chronic, severe, and medically-refractory psychiatric disorders. In this context, only capsulotomy can have fewer adverse effects and complications.[15] New minimally invasive techniques, such as MRgFUS, have the advantage of avoiding skull opening and, thus, relevant complications, such as hemorrhage and infections, can be avoided.[3] With the ongoing progress in modern neuroimaging techniques, future studies should focus on whether specific complications are associated with specific ALIC parts/tracts. This knowledge could enable safer targeting and improve the capsulotomy's safety profile.

Finally, ethics committee approval is a critical part of the design and execution of capsulotomy studies. Given that this is a last-resort procedure to manage a patient's illness that is refractory to all other treatments, appropriate institutional ethics approval is of paramount importance, along with careful study design. As with other treatment methods, explanation of potential complications and side effects to patients and their families is mandatory before making any decision to proceed.

As expected, this systematic review has several limitations. Its principal limitation is the fact that many of the included studies are case reports or case series, and data from other reviews have also been used. As a result, the total number of patients who underwent capsulotomy is restricted. Further studies, ideally multicentric, would be required in order to reach safer conclusions.

Conclusion

Capsulotomy is a lesioning procedure targeting the internal capsule in the treatment of specific severe, treatment-resistant psychiatric disorders, mainly OCD. The modalities used for this procedure are RF ablation, GKRS, and MRgFUS. Postoperative complications are usually

transient and self-regressing. These include neurological and psychiatric manifestations, cerebrovascular accidents, thromboembolic events, and infections. Urinary incontinence, sleep disorders, fatigue, and disorientation are frequent but transient complications of RF lesioning. Its long-term complications include bulimia, memory loss, and personality changes. Gamma capsulotomy has the risk of adverse radiation effects, such as radiation necrosis, brain edema, and cyst formation. MRgFUS seems to lack many of the inherent risks associated with more invasive treatment modalities. Further clinical research is key to the safety of the capsulotomy.

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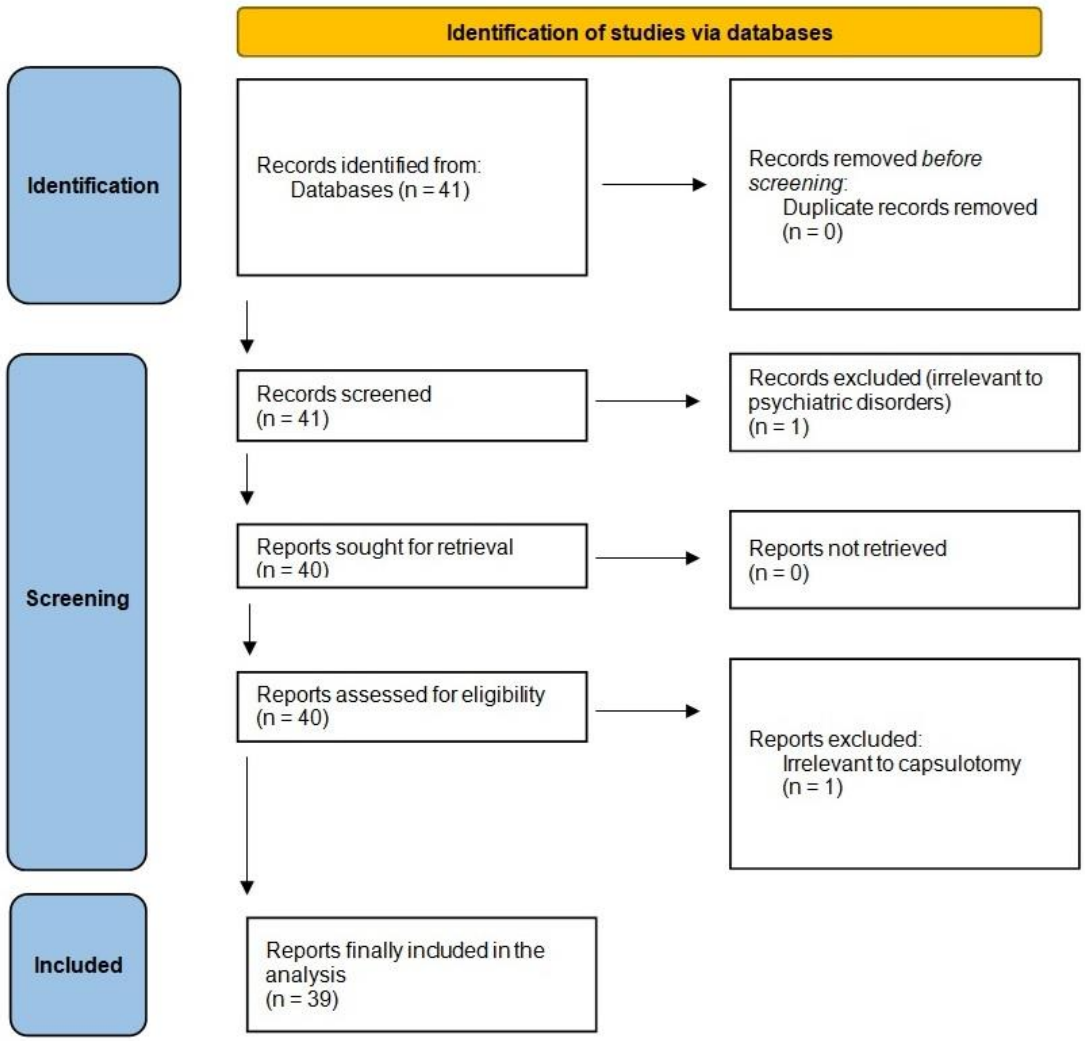

Figure 1. Article selection process of our analysis (PRISMA diagram)

Table 1. Summary of clinical data regarding indication, sample, method, and complications of capsulotomy as a treatment option for psychiatric disorders

Authors (year)	**Disease**	**Number of patients**	**Lesioning method**	**Complications / comments**
Lippitz et al. (1997)[13]	OCD	22	RF	Lesions within the group of patients with poor outcome (n = 5) were located elsewhere, mostly further anterior in the internal capsule
Happe et al. (2001)[18]	Bipolar affective disorder	1	RF	Impaired theory of mind

Ruck et al. (2006)[21]	Anxiety	16	RF	Impairment of executive functions, apathy
Ruck et al. (2008)[5]	OCD	25	RF or GKRS	Weight gain, executive dysfunction, apathy, disinhibition, memory problems, incontinence, seizures
Barbier et al. (2011)[9]	Anorexia nervosa and OCD	1	RF	Transient bradycardia with accelerated junctional rhythm at rest, mild disorientation in place or time, moderate somnolence, slowed thinking, loss of concentration, apathy, emotional emptiness, mild loss of decorum
Christmas et al. (2011)[19]	Major depression	20	RF	Urinary incontinence, nausea, dizziness, headache, confusion, ataxia, concentration problems, memory problems, loss of motivation, tiredness, somnolence, seizures, weight gain, subjective personality change, lack of emotional response, addiction
Jimenez et al. (2012)[22]	Aggressive behavior	10	GKRS	Disinhibition, somnolence in the immediate postoperative period, and paraparesis
D'Astous et al. (2013)[11]	OCD	19	Mechanical lesioning using a Bertrand leucotome	Frontal syndrome, urinary incontinence, pneumonia, urinary infection, hemiplegia due to perioperative hemorrhage, cognitive impairment
Liu et al. (2014)[23]	Schizophrenia	116	RF	Urinary incontinence (18), disorientation (4), sleep disorder (12), fatigue (10). These symptoms usually disappeared within two weeks. Long-term complications: bulimia (9), memory loss (7), personality changes (6), lazy behavior (5), hypererotism (4). One patient had slight bleeding and recovered without reoperation. One patient had a seizure and was controlled with antiepileptic medication
Batistuzzo et al. (2015)[26]	OCD	16	GKRS	One patient developed an asymptomatic radionecrotic cyst later during follow-up

Liu et al. (2018)[29]	Anorexia nervosa	74	RF	Common short-term side effects: urinary incontinence (9.5%), sleep disorders (10.8%), fatigue (8.1%). Long-term complications: disinhibition (8.1%), memory loss (4.1%), lethargy (5.4%)
Kim et al. (2018)[27]	OCD	11	MRgFUS	Headache and vestibular symptoms (mild and transient)
Huang et al. (2019)[30]	Epilepsy and severe* psychopatholo gy	13	RF	Headache, confusion, transient memory deficits, weight gain
Gupta et al. (2019)[24]	OCD	40	GKRS	Mood disturbance (25%), worsening in Yale-Brown Obsessive-Compulsive Scale scores (7.5%), neurological complications (7.5%). One patient developed radiation necrosis with edema that improved with steroids.
Jung et al. (2019)[31]	OCD	4	MRgFUS	None reported
Krámská et al (2021)[32]	OCD	12	RF	None reported
Kasabkojian et al. (2021)[25]	OCD	1	GKRS	Manic episode, cognitive memory changes, visual hallucinations, confabulation, frontal lobe symptoms, hemispheric edema, small cyst

**Mainly positive psychotic symptoms, as well as aggression and excessive impulsivity, followed by anxiety, depression, and intellectual disability. GKRS: Gamma Knife radiosurgery; MRgFUS: magnetic resonance-guided focused ultrasound; OCD: Obsessive-Compulsive Disorder; RF: radiofrequency*

PSYCHIATRIKI

ΑΝΑΣΚΟΠΗΣΗ

Επιπλοκές της καψοτομής στη θεραπεία των ψυχιατρικών διαταραχών: Συστηματική ανασκόπηση

Ιωάννης Ν. Μαυρίδης,[1] Ευστράτιος-Στυλιανός Πυργελής[2]

1. *Πανεπιστημιακή Νευροχειρουργική Κλινική, Τμήμα Ιατρικής, Σχολή Επιστημών Υγείας, Δημοκρίτειο Πανεπιστήμιο Θράκης, Αλεξανδρούπολη, Ελλάδα*
2. *Α΄ Νευρολογική Κλινική, Τμήμα Ιατρικής, Σχολή Επιστημών Υγείας, Εθνικό και Καποδιστριακό Πανεπιστήμιο Αθηνών, «Αιγινήτειο» Νοσοκομείο, Αθήνα, Ελλάδα*

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----------**ΠΕΡΙΛΗΨΗ**----------

Για περισσότερο από μισό αιώνα, στερεοτακτικές νευροχειρουργικές επεμβάσεις χρησιμοποιούνται για τη θεραπεία ασθενών με σοβαρά, εξαντλητικά συμπτώματα φαρμακοανθεκτικών ψυχιατρικών διαταραχών όπως η ιδεοψυχαναγκαστική διαταραχή (OCD). Τέτοιες χειρουργικές παρεμβάσεις περιλαμβάνουν τεχνικές διέγερσης και ιστικής καταστροφής (lesioning). Η καψοτομή είναι μια τεχνική ιστικής καταστροφής που στοχεύει την έσω κάψα. Ο σκοπός αυτής της συστηματικής ανασκόπησης είναι να εξετάσει την ασφάλεια της καψοτομής στη θεραπεία σοβαρών φαρμακοανθεκτικών ψυχιατρικών διαταραχών, εστιάζοντας στις επιπλοκές της. Μεθοδολογικά, έγινε βιβλιογραφική έρευνα χρησιμοποιώντας του όρους «ψυχιατρικός», «καψοτομή» και «επιπλοκές» στη βάση δεδομένων PubMed/Medline μέχρι το τέλος του 2022. Η αναζήτηση απέδωσε 41 αποτελέσματα. Μετά από έλεγχο δυνητικής καταλληλόλητας, 39 άρθρα σχετικά με το θέμα αναλύθηκαν περαιτέρω και χρησιμοποιήθηκαν τελικά για αυτήν την ανασκόπηση. Δε χρησιμοποιήθηκε ειδικό εργαλείο αξιολόγησης για τον κίνδυνο μεροληψίας σε αυτήν τη μελέτη. Η μεγάλη πλειονότητα των δεδομένων καψοτομής στη βιβλιογραφία προέρχεται από ασθενείς με OCD και οι κύριες μέθοδοι που χρησιμοποιούνται για αυτήν την επέμβαση είναι η κατάλυση με ραδιοσυχνότητες (RF), η ακτινοχειρουργική με γ-Knife (GKRS) και ο καθοδηγούμενος από μαγνητική τομογραφία εστιασμένος υπέρηχος (MRgFUS). Οι μετεγχειρητικές επιπλοκές είναι συνήθως παροδικές και αυτοπεριοριζόμενες. Αυτές περιλαμβάνουν νευρολογικές και ψυχιατρικές εκδηλώσεις, αγγειακά εγκεφαλικά επεισόδια, θρομβοεμβολικά επεισόδια και λοιμώξεις (αναπνευστικού, ουροποιητικού). Συνήθεις επιπλοκές είναι η κεφαλαλγία, το τοπικό οίδημα και το μετωπιαίο σύνδρομο. Άλλες επιπλοκές περιλαμβάνουν την αταξία, τις επιληπτικές κρίσεις, την ακράτεια ούρων, την αύξηση του βάρους και την κόπωση. Σχετικά με τις διαφορετικές τεχνικές, η ακράτεια ούρων, οι διαταραχές ύπνου, η κόπωση και ο αποπροσανατολισμός είναι συχνές αλλά παροδικές επιπλοκές της RF ιστικής καταστροφής. Η γ-καψοτομή ενέχει τον κίνδυνο ανεπιθύμητων ενεργειών της ακτινοβολίας, όπως η ακτινονέκρωση, το εγκεφαλικό οίδημα και ο σχηματισμός κύστεων. Ο MRgFUS φαίνεται να στερείται μερικών από τους εγγενείς κινδύνους των πιο επεμβατικών μεθόδων. Οι επιπλοκές της καψοτομής, συνήθως παροδικές και αυτοπεριοριζόμενες, περιλαμβάνουν νευρολογικές και ψυχιατρικές εκδηλώσεις, αγγειακά εγκεφαλικά επεισόδια, θρομβοεμβολικά επεισόδια και λοιμώξεις. Η εμφάνιση και η φύση τους εξαρτάται συνήθως από την επιλεχθείσα τεχνική. Ο κύριος περιορισμός αυτής της μελέτης είναι το γεγονός ότι πολλές μελέτες που περιλαμβάνονται είναι αναφορές περιστατικών και σειρών ασθενών. Ως αποτέλεσμα, ο συνολικός αριθμός των ασθενών που υποβλήθηκαν σε καψοτομή είναι περιορισμένος. Περαιτέρω έρευνα είναι αναγκαία ώστε να

βελτιωθεί περισσότερο η ασφάλεια της καψοτομής. Δεν ελήφθη χρηματοδότηση για την παρούσα ανασκόπηση.

ΛΕΞΕΙΣ ΕΥΡΕΤΗΡΙΟΥ: γ-Knife, επιπλοκές, έσω κάψα, ιδεοψυχαναγκαστική διαταραχή, καψοτομή.

Επιμελητής συγγραφέας: Ιωάννης Ν. Μαυρίδης, Πανεπιστημιακή Νευροχειρουργική Κλινική, Τμήμα Ιατρικής, Σχολή Επιστημών Υγείας, Δημοκρίτειο Πανεπιστήμιο Θράκης, Πανεπιστημιακό Γενικό Νοσοκομείο Αλεξανδρούπολης, Δραγάνα, 68 100 Αλεξανδρούπολη, Ελλάδα, Email: inmavridis@gmail.com