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UM ESTUDO SOBRE A NEUROMODULAÇÃO NO TRANSTORNO OBSESSIVO-COMPULSIVO

RIO DE JANEIRO

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Dissertação de mestrado submetida ao corpo docente do Programa de Pós-graduação em Psiquiatria e Saúde Mental – PROPSAM – do Instituto de Psiquiatria da Universidade Federal do Rio de Janeiro, como parte dos requesitos necessários para obtenção do Grau de Mestre em Psiquiatria.

Orientador:Leonardo Franklin da Costa Fontenelle

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RIO DE JANEIRO

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Aos meus pais que sempre incentivam o meu crescimento pessoal e profissional.

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Resumo

O Transtorno Obsessivo-Compulsivo (TOC) caracteriza-se pela presença de obsessões que trazem ao paciente sensações como nojo, repulsa e culpa, e são aliviadas ou atenuadas por meio de compulsões, muitas vezes, realizadas de forma extenuante. O tratamento proposto como primeira linha para o TOC inclui o uso de inibidores seletivos de recaptação de serotonina (ISRSs). Normalmente, são utilizados na maior dose tolerada, associados ou não à antipsicóticos. Em média, 40% a 60% dos pacientes são resistentes a este método (IRS). Entretanto, quando a farmacoterapia é associada às terapias de exposição e prevenção de resposta (EPR), o número de pacientes resistentes ao tratamento é reduzido para 30%. Sendo o TOC uma enfermidade consideravelmente prevalente e com prognóstico ainda desfavorável, o objetivo desta dissertação é explorar alguns recursos neuromodulatórios de relevância na prática clínica, discutindo as diretrizes atuais e futuras a respeito do uso dos mesmos no transtorno em questão. São estes: (1) Estimulação Cerebral Profunda (ECP); (2) Eletroconvulsoterapia (ECT) ;(3) Estimulação Magnética Transcraniana (EMT); e (4) Estimulação Elétrica por Corrente Contínua (ETCC). Em seguida, serão apresentados quatro artigos que compõem esta dissertação: o primeiro artigo, “Eletroconvulsivetherapy for Obsessive-Compulsive Disorder: A Systematic Review,” é uma revisão sistemática de eletroconvulsoterapia no TOC que incluiu 50 artigos, a maioria relatos de casos; o segundo artigo, “Eletroconvulsive therapy in Obsessive-Compulsive Disorder: A Chart Review and Evaluation of Its Potential Therapeutic Effects,” é uma série de casos que inclui 5 pacientes do ambulatório de TOC do IPUB/UFRJ que realizaram ECT; o terceiro artigo intitulado: “Prevalencea nd Correlates of Electroconvulsive Therapy Delivery in Outpatients with Obsessive-Compulsive Disorder,” é um estudo que fez a análise de um banco de dados de 1001 pacientes com TOC, de sete centros especializados diferentes e o quarto artigo, “An Interim Analysis of a Double-Blind Sham-Controlled Study on the Acute Effects of Transcranial Direct Current Stimulation in Obsessive-CompulsiveDisorder,” representa os resultados preliminares de um ensaio clínico controlado quasi-randomizado, duplo-cego, utilizando a ETCC em pacientes do ambulatório IPUB/UFRJ com TOC. A partir do estudo realizado, constatou-se que, até o momento, a ECP é o método neuromodulatório mais promissor no TOC, mas investimentos científicos estão sendo realizados em métodos não-invasivos de abordagem mais focal do que a ECT.

Palavras-chave: transtorno obsessivo-compulsivo; estimulação cerebral profunda; eletroconvulsoterapia; estimulação magnética transcraniana; estimulação transcraniana por corrente contínua

Abstract

Obsessive-compulsive disorder (OCD) is characterized by the presence of obsessions which bring feelings of disgust, repulse or guilt to the patient and are alleviated or diminished through compulsions that are often executed in a tiresome basis. First-line treatment of OCD includes the administration of selective serotonin reuptake inhibitors (SSRIs). It´s commonly used the highest tolerated dosage, associated or not with antipsychotics. An average of 40 to 60% of the patients shows poor results to the SSRIs treatment. When pharmacotherapy is associated to exposure and response prevention behavioral treatment (ERP), this rate reduced to 30%. Being OCD a reasonably prevalent illness, with still unlikely prognosis, this thesis´ aim is to explore some relevant neuromodulatory methods in the clinical practice and discuss current and future guidelines to that disorder using those methods. They are: (1) Deep Brain Stimulation (DBS); (2) Electroconvulsive Therapy (ECT); (3) Transcranial Magnetic Stimulation (TMS); and (4) Transcranial Direct Current Stimulation (TDCS). Then, there will be presented four articles that compose this thesis. The first one, "Electroconvulsive therapy for obsessive-compulsive disorder: a systematic review", is a systematic review of ECT for OCD which includes 50 articles, most of them case reports. The second paper, "Electroconvulsive Therapy in Obsessive-Compulsive Disorder: A Chart Review and Evaluation of Its Potential Therapeutic Effects" is a case series that includes five patients from the OCD Ambulatory of IPUB/UFRJ who were submitted to ECT. The third article, named "Prevalence and Correlates of Electroconvulsive Therapy Delivery in Outpatients with Obsessive-Compulsive Disorder", is a study that analyzed a databank of 1001 OCD patients, from seven different specialized centers. The fourth article, "An Interim Analysis of a Double-Blind Sham-Controlled Study on the Acute Effects of Transcranial Direct Current Stimulation in Obsessive-Compulsive Disorder" shows the preliminary results of a double blind, sham-controlled clinical assay, applying TDCS in OCD patients from the ambulatory of IPUB/UFRJ.From the study, we found that, to date, the ECP is the most promising neuromodulatory method in OCD, but scientific investments are being conducted in non-invasive methods of more focal approach than ECT.

Key-words: obsessive-compulsive disorder; deep brain stimulation; electroconvulsive therapy; transcranial magnetic stimulation; transcranial direct current stimulation

LISTA DE SIGLAS

AMS – Área Motora Suplementar

CGI – do inglês, *Clinical Global Impression*

CMF – Córtex Médio-Frontal

COF – Córtex Órbito-Frontal

CPFDL- Córtex Pré-Frontal Dorsolateral

CTEC – Cortico-Talâmico-Estriado-Cortical

CV/EV – Cápsula Ventral/Estriado Ventral

ECP – Estimulação Cerebral Profunda

ECT - Eletroconvulsoterapia

EMT – Estimulação Magnética Transcraniana

EMTR – Estimulação Magnética Transcraniana Repetitiva

EPR – Exposição e Prevenção de Resposta

ETCC – Estimulação Transcraniana por Corrente Contínua

IRS – Inibidor de Recaptação de Serotonina

ISRS – Inibidor Seletivo de Recaptação de Serotonina

NAC – Núcleo Accumbens

NST – Núcleo Subtalâmico

PTI – Pedúnculo Talâmico Inferior

TAB – Transtorno Afetivo Bipolar

TEP – Tomografia por Emissão de Pósitrons

TOC – Transtorno Obsessivo-Compulsivo

YBOCS – do inglês, *Yale-Brown Obsessive-CompulsiveScale*

Nesta lista constam somente siglas não-esclarecidas nos artigos desta dissertação.

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1. INTRODUÇÃO

O Transtorno Obsessivo-Compulsivo (TOC) é um transtorno mental de curso crônico, com prevalência na população geral entre 0,3% e 3,1% (FONTENELLE; MENDLOWICZ; VERSIANI, 2006), capaz de proporcionar intenso sofrimento psíquico ao paciente e acarretar graves prejuízos no âmbito social, profissional e pessoal. O TOC caracteriza-se pela presença de obsessões (pensamentos, impulsos ou imagens) repetitivas e intrusivas que trazem ao paciente sensações como nojo, repulsa e culpa, e são aliviadas ou atenuadas através de compulsões (comportamentos ou rituais mentais), muitas vezes, realizadas de forma extenuante. (APA,2 013; MIGUEL; GENTIL; GATTAZ, 2011). Os sintomas obsessivos-compulsivos possuem apresentações heterogêneas, divididas em subtipos, que demonstram a complexidade da doença. Estas dimensões são caracterizadas mais comumente como contaminação/lavagem, sexual/religioso, agressão/checagem, simetria/ordenamento, colecionismo. (MATAIX-COLS; ROSARIO-CAMPOS; LECKMAN, 2005)

O tratamento proposto como primeira linha para o TOC inclui o uso de inibidores seletivos de recaptação de serotonina (ISRS), sendo os aprovados: fluoxetina (40-60 mg/dia), fluvoxamina (até 300mg/dia), sertralina (até 200mg/dia), paroxetina (até 60mg/dia), escitalopram (até 40mg/dia) e citalopram (40-60 mg/dia) ou a clomipramina (até 250 mg/dia), que é um inibidor não seletivo da recaptação de serotonina (PRACTICE GUIDELINE-APA, 2007). Normalmente, são utilizados na maior dose tolerada, associados ou não à antipsicóticos (SEIBELL; HOLLANDER, 2014). Em média, 40% a 60% dos pacientes são resistentes ao tratamento com inibidores de recaptação de serotonina (IRSs) (PALLANTI; QUERCIOLI, 2006).

No entanto, quando a farmacoterapia é associada às terapias de exposição e prevenção de resposta (EPR), o número de pacientes resistentes ao tratamento é reduzido para 30% (SCHRUERS et al., 2005). Na prática clínica e em pesquisas científicas, a responsividade do paciente com TOC ao tratamento convencional pode ser avaliada de forma objetiva através da escala de Impressão Clínica Global (*Clinical Global Impression* – CGI) e, principalmente, pela escala de sintomas obsessivos-compulsivos de Yale-Brown (*Yale-Brown Obsessive-CompulsiveScale* – YBOCS). O enfermo é considerado não-responsivo quando apresenta um escore no CGI igual a seis e uma redução no escore de YBOCS menor do que 25%. (PALLANTI; QUERCIOLI, 2006)

A partir dos pacientes não-respondedores ao tratamento de primeira linha, surge a expectativa no meio científico de avanços nos métodos de neuroestimulação, principalmente, não-invasivos. Para que se tenha progresso com as técnicas neuromodulatórias no TOC, é fundamental aprofundar o conhecimento a respeito da fisiopatologia deste transtorno mental. Por meio de estudos de neuroimagem funcional, foi possível identificar que neste transtorno há uma hiperatividade no circuito córtico-talâmico-estriado-cortical (CTEC), envolvendo principalmente o córtex órbito-frontal, córtex pré-frontal dorsolateral, giro do cíngulo anterior e gânglios da base (ARONSON; KATNANI; ESKANDAR, 2014).

A hiperexcitabilidade do circuito CTEC se dá por haver um desequilíbrio das conexões entre as regiões corticais e subcorticais que ocorre através de projeções glutamatérgicas (excitatórias) e gabaérgicas (inibitórias), por vias diretas e indiretas (LAPIDUS et al., 2014). O córtex médio-frontal (CMF), que engloba a região dorsal do cingulado anterior, e a área motora suplementar (AMS), também estão hiperexcitados no TOC. Nesse sentido, a hiperexcitabilidade do CMF pode estar relacionada a mecanismos compensatórios (YÜCEL et al., 2007) e ser uma alteração relacionada ao endofenótipo. (DE WIT et al., 2012).

Esta dissertação apresentará quatro métodos neuroestimulatórios de relevância na prática psiquiátrica, com o objetivo de discutir o que é proposto atualmente na literatura em relação ao TOC e também as diretrizes futuras. São estes métodos: (1) Estimulação Cerebral Profunda (ECP); (2) Eletroconvulsoterapia (ECT); (3) Estimulação Magnética Transcraniana (EMT); e (4) Estimulação Elétrica por Corrente Contínua (ETCC).

1.1 ESTIMULAÇÃO CEREBRAL PROFUNDA (ECP)

Aprovada em 2009 pelo *Food and Drug Administration* como método cirúrgico para o tratamento do TOC (YOUNGERMAN et al., 2016), a estimulação cerebral profunda (ECP) tem caráter invasivo, mas promove um efeito neuromodulatório reversível. Ainda na década de 80, começou a ser utilizada para o tratamento de casos refratários da doença de parkinson, tremores e distonias (DA CUNHA et al., 2015). Através do auxílio de neuronavegação, eletrodos podem ser posicionados em diferentes áreas relacionadas ao circuito cortico-talâmico-estriado-cortical, nas regiões referentes ao córtex orbito-frontal, tálamo, núcleo caudado, estriado ventral e giro do cíngulo anterior. Em seguida, um aparelho implantado no subcutâneo da região subclavicular ou abdominal irá emitir pulsos responsáveis por gerar o estímulo. A primeira parte da cirurgia é feita com o paciente acordado sendo capaz, dessa forma, de avaliar possíveis efeitos adversos, porém a segunda etapa é realizada com o paciente sob anestesia geral, quando então o gerador

de pulsos é inserido. Conecta-se este aparelho a ECP por meio de fios encapsulados. (TIERNEY et al., 2013; BLOMSTED et al., 2013). A reversibilidade do método é garantida pela possibilidade de ligar e desligar o aparelho e rever os parâmetros de estimulação, ainda com os eletrodos implantados no paciente. (GREENBERG; RAUCH; HABER, 2010).

As regiões citadas fazem parte de uma complexa rede de neurocircuitos envolvidos na fisiopatologia do TOC. Neste distúrbio, há um desequilíbrio no circuito que promove uma hiperexcitabilidade no sistema CTEC. Através de um estudo com tomografia por emissão de pósitrons (TEP) foi possível identificar aumento do metabolismo de glicose em córtex orbito-frontal, e núcleo caudado (BAXTER et al., 1988). A atividade metabólica aumentada no estriado exacerba a inibição do neurofeedback negativo, e as áreas fronto-corticais mantêm-se hiperativas (ARONSON; KATNANI; ESKANDER, 2014). A ECP gera uma inibição deste sistema (BLOMSTED et al., 2013). No entanto, ainda há muitos questionamentos a respeito de quais áreas adjacentes ao alvo da ECP irão atuar nesta neuromodulação e de que forma, pois há poucos estudos controlados-randomizados referentes à estimulação profunda no TOC (DA CUNHA et al., 2015). Nesse sentido, os métodos cirúrgicos que provocam lesões ablativas irreversíveis foram fundamentais para o norteio dos primeiros alvos da ECP.

Baseando-se nos resultados satisfatórios da capsulotomia ablativa, a primeira região a ser estimulada, utilizando-se a ECP, foi a região límbica anterior da cápsula interna. Nuttin e colaboradores (1999) publicaram a primeira pesquisa de ECP no TOC, propondo um método de estimulação bilateral reversível que mostrou benefício durante duas semanas de estimulação. Percebendo que o aumento do tempo dessa atividade poderia trazer melhores resultados, realizaram outro estudo, desta vez duplo-cego controlado-randomizado com seis pacientes (NUTTIN et al., 2003). Após três meses de ECP, encontraram uma redução no escore do YBOCS de 35%. Outro alvo utilizado em alguns estudos, tanto unilateralmente como bilateralmente, é o núcleo accumbens (NAC), por sua proximidade com a região límbica anterior da cápsula interna. Muitas vezes, a estimulação de uma região pode alcançar uma área adjacente, funcionando como um único alvo (BLOMSTED et al., 2013). Denys e colaboradores (2010) estimularam a NAC bilateralmente, através da realização de um ensaio clínico com dezesseis pacientes que incluiu três fases. A fase inicial durou oito meses e foi um estudo aberto. Houve uma redução de 46% no escore de YBOCS; a fase seguinte consistiu em um estudo duplo-cego controlado-randomizado, com duas etapas de duas semanas de duração, e uma redução de 25% no escore total de YBOCS. Por último, o tratamento foi mantido por 12 meses e durante este processo houve manutenção da redução dos escores de YBOCS e nas escalas de depressão e ansiedade.

A partir do conhecimento de áreas adjacentes ao estriado, um novo alvo passou a ser utilizado; a região da cápsula ventral/estriado ventral (CV/EV), correspondente à porção mais anterior da cápsula interna. Essa representa o local onde as fibras do circuito CTEC se condensam. Várias pesquisas de neuroimagem funcional defendem a hipótese de que a CV/EV corresponde à região envolvida nos neurocircuitos relacionados ao TOC (GREENBERG; RAUCH; HABER, 2010). Um estudo de 2010, que publicou resultados dos últimos oito anos, encontrou melhora dos sintomas obsessivos-compulsivos em dois terços da amostra com a estimulação da CV/EV. Constatou-se ainda que o aprimoramento da técnica e a priorização de regiões cada vez mais póstero-inferiores da CV/EV, ao longo dos anos, refletiu na resposta clínica dos pacientes; aqueles que realizaram o procedimento nos primeiros anos obtiveram uma redução de até 30% no YBOCS, contudo os que passaram por este processo, nos últimos anos, obtiveram uma redução de até 70% no escore de YBOCS (GREENBERGet al., 2010).

Outra área promissora, porém, ainda em fase experimental, é o pedúnculo talâmico inferior (PTI), que conecta o núcleo talâmico ao córtex órbito-frontal (CLEARLY et al., 2015). Um ensaio clínico aberto, com cinco pacientes, realizou a ECP bilateralmente no PTI, pelo período de doze meses (JIMENEZ-PONCE et al., 2009). Após este período, houve uma redução média no escore do YBOCS de 35 para 17,8 pontos. Destacado destas regiões citadas há o núcleo subtalâmico (NST), que integra o sistema límbico associativo e as funções motoras. (MORISHITA et al., 2014; CLEARLY et al., 2015). A estimulação de porções ventro-mediais e mediais do NST ativam o sistema dopaminérgico e serotoninérgico. Todavia, em pacientes com doença de parkinson, notava-se melhora em sintomas do humor, ansiedade (LAPIDUS et al., 2014) e sintomas obsessivos-compulsivos (MALLET et al., 2002). Um ensaio clínico duplo-cego controlado-randomizado provocou o estímulo no NST de oito pacientes com TOC por dez meses. Após esta ação, o escore de YBOCS foi significativamente menor em pacientes do grupo ativo, quando comparados ao grupo placebo. No entanto, ocorreram quinze efeitos adversos graves, incluindo uma hemorragia intracerebral (MALLET et al., 2008).

Portanto, por ser um método invasivo que envolve a craniotomia e mantém orifícios permanentemente abertos durante a sua utilização, pode causar efeitos adversos inerentes à cirurgia (DENYS et al., 2010; MALLET et al., 2008). As complicações cirúrgicas mais comuns são as infecções no local do implante e as hemorragias intracranianas, que podem ocorrer em 3 a 15% dos casos, assim como convulsões e infarto agudo do miocárdio. Apenas 0,5% a 1% dos casos levam à morte ou complicações neurológicas graves (SEDRAK et al., 2013), ainda assim, este percentual é menor em relação às cirurgias convencionais e ablativas. O efeito colateral mais comum que tem possibilidade de acontecer, em decorrência de estímulos cronicamente de

alta frequência, são os sintomas da hipomania, principalmente quando o alvo estimulado é o NST (LAPIDUS et al., 2014). Também surgiram em outros casos depressão com maior risco de suicidabilidade, porém, em sua maioria, os sintomas relacionados ao humor foram revertidos com o reajuste dos parâmetros (TIERNEY et al., 2013).

Diante dos riscos apresentados e da complexidade deste método neuromodulatório, os critérios de elegibilidade dos pacientes a serem submetidos ao procedimento devem ser bem rigorosos (GRANT et al., 2014). A indicação para realizar a ECP deve ser feita por um psiquiatra, mas, em seguida, avaliado por um comitê multidisciplinar composto por neurocirurgiões, psicólogos e enfermeiros (TIERNEY et al., 2013; GRANT et al., 2014). Dentre os critérios de inclusão estão: (1) escore na escala de sintomas obsessivos-compulsivos de Yale-Brown (YBOCS) > 30; (2) mais de três meses utilizando as máximas doses toleradas de pelo menos três inibidores de recaptação de serotonina (IRSs), sendo um deles a clomipramina, associados ou não a um antipsicótico; (3) falha no tratamento com terapias comportamentais (> 20 sessões), (TIERNEY et al., 2013; BLOMSTED et al., 2013). Pacientes menores de 18 anos, gestantes, usuários de drogas que tenham feito consumo no último ano, pessoas que possuem outra patologia grave de eixo I (transtorno afetivo bipolar, esquizofrenia) e lesões neurológicas como acidente vascular cerebral, epilepsia e aneurisma são considerados não-elegíveis (TIERNEY et al., 2013).

Normalmente, estes pacientes são acompanhados por períodos superiores a três meses, e os resultados satisfatórios e desejados podem demorar até um ano para serem identificados. O prognóstico é mensurado a partir da escala de YBOCS, que avalia a gravidade dos sintomas obsessivos-compulsivos relacionados ao TOC. São considerados bem-sucedidos os tratamentos com a ECP que promovem pelo menos 35% de redução no YBOCS (GREENBERG; RAUCH; HABER, 2010). Pepper, Hariz e Zrinzo (2015) realizaram uma revisão sistemática comparando a capsulotomia anterior à ECP com alvo nas regiões da CV/EV e no NAC. Sendo assim, avaliaram se existia superioridade de um método em relação ao outro no que diz respeito ao número de resultados bem-sucedidos. Apesar de aparente supremacia da capsulotomia em relação à ECP, é importante ressaltar que o perfil de gravidade dos pacientes que fizeram a cirurgia ablativa era de moderada a grave, e os que realizaram a estimulação cerebral profunda possuíam quadros graves a severos. Além disso, há experiência de muitos anos no meio cirúrgico com as cirurgias ablativas, enquanto a ECP é utilizada há cerca de uma década.

É de suma importância destacar que a ECP deve ser indicada de forma bem criteriosa, pois possui efeitos adversos que não podem ser desprezados. Pessoas com distúrbios da coagulação ou que são mais propensas a infecções podem ser candidatas à capsulotomia ou a

outra cirurgia por radiofrequência (TIERNEY et al., 2013). Para realizar a ECP, o paciente precisa estar disponível para ir, frequentemente, aos centros de referência, realizar ajustes de parâmetros e avaliação de resultados. Outra limitação ainda existente no uso contínuo da estimulação profunda é a baixa durabilidade das baterias geradoras de pulsos: quanto maior a frequência desses, mais rápido ocorre a depleção das baterias e o paciente é submetido a novo processo invasivo. Atualmente, alguns centros já dispõem de baterias autocarregáveis, mas ainda pouco viabilizadas devido a um maior custo (GREENBERG, 2010). Deve-se considerar que apesar da ECP ter sido aprovada para uso no tratamento do TOC, ainda não é um método padronizado (MORISHITA et al., 2014).

1.2 ELETROCONVULSOTERAPIA (ECT)

A eletroconvulsoterapia (ECT) é uma técnica neuromodulatória realizada há mais de oitenta anos e que revolucionou o tratamento psiquiátrico na década de quarenta (MCCALL; KELLNER; FINK, 2014). Nesta época, a estratégia foi responsável por promover um novo prognóstico a muitos pacientes com o diagnóstico de esquizofrenia e outros transtornos mentais de curso crônico e de difícil controle. Nos anos 60, com o advento da fabricação de psicofármacos e início de seu uso, ocorreu uma considerável redução da prática da ECT. No entanto, logo percebeu-se que muitos quadros psicóticos e de depressão apenas remitiam satisfatoriamente com a eletroconvulsoterapia. (FINK, 2014). Ainda hoje, é o tratamento de primeira escolha nos casos de depressão com risco de suicídio e/ou presença de quadro psicótico, catatonia e mania grave, prolongada (SALLEH et al., 2006). Nos casos de depressão refratários aos tratamentos farmacológicos e psicoterápicos, há uma taxa de sucesso da ECT de 80% (ABBOTT et al. ,2014).

Apesar da estigmatização que ainda permeia e retarda as indicações para realização da ECT (MEDDA; TONI; PERUGI, 2014; GEDULDIG; KELLNER, 2016), a técnica é eficaz e segura, com uma mortalidade que atinge cerca de 1 a cada 100.000 pacientes (TAYLOR,2007; SALLEH et al., 2006). Embora alguns países não sigam as recomendações de guidelines para a realização da ECT (LEIKNES; SCHWEDER; HOIE, 2012), desde a década de 50, é preconizado que o paciente seja submetido às convulsões mediante o uso de relaxantes musculares, sedação anestésica e ventilação das vias aéreas (GALLEGOS et al., 2012). Antes mesmo de realizar o procedimento, a pessoa deve assinar um termo de consentimento esclarecido e realizar exames laboratoriais, eletrocardiograma e radiografia de tórax, caso possua doenças cardíacas ou pulmonares (PERIZZOLO et al., 2003). São feitas também

recomendações quanto às medicações que devem ser evitadas na véspera, como anticonvulsivantes, benzodiazepínicos e o lítio (TAYLOR, 2007). O efeito colateral mais preocupante e ainda alvo de pesquisas científicas é a perda cognitiva. Embora, na maioria dos casos, a amnésia anterógrada e a dificuldade de adquirir novas memórias sejam efeitos transitórios, é uma preocupação recorrente, mais frequente na aplicação bilateral. (SALLEH et al., 2006).

Nos últimos anos, alguns estudos envolvendo neuroimagem funcional e estrutural demonstraram possíveis efeitos da ECT na neuroplasticidade, apesar de ainda não se saber com precisão o mecanismo deste processo (BOUCKAERT et al., 2014; ABBOTT et al., 2014). Pesquisas indicam que o efeito neuromodulatório da ECT promove um aumento da atividade serotoninérgica, aumentando o número de receptores 5HT1a e 5HT2a na fenda pós-sináptica do hipocampo e em regiões corticais. Atua também no sistema dopaminérgico, o que pode induzir estresse, ativando o sistema hipotálamo-pituitária-adrenal, mas contribuí para melhorar a concentração, motivação e atenção, favorecendo a redução dos sintomas relacionados à depressão e à ansiedade (BALDINGER et al., 2014).

Ainda que a ECT tenha seu papel bem determinado e consagrado em casos graves e refratários de depressão unipolar, transtorno afetivo bipolar (TAB), alguns casos de esquizofrenia e, mais recentemente, em grupos específicos como gestantes (LEIKNES et al., 2015) e idosos (GEDULDIG; KELLNER, 2016) não há evidências científicas que sustentem a sua indicação no TOC. Como será apresentada, a literatura é composta por muitos relatos de casos ou série de casos que, apesar de terem descrito tratamentos eletroconvulsivos eficazes, não trazem consistência metodológica. Outro dado relevante é o fato de que em muitos estudos os pacientes não foram adequadamente tratados com IRSs e/ou outros procedimentos complementares, e em alguns desses estudos isso também ocorre porque os enfermos foram tratados antes do surgimento do tratamento farmacológico padrão-ouro no TOC (FONTENELLE et al., 2015).

Algumas pesquisas de revisão a respeito do tema, publicados nos últimos dez anos, questionam um possível viés de publicação, pois traz estranheza o fato de apenas terem sido publicados resultados positivos, mas existir um consenso entre os protocolos clínicos de não-inclusão da ECT como método terapêutico nos casos de TOC grave e refratário (FONTENELLE et al., 2015). Em um estudo retrospectivo realizado pelo nosso grupo de pesquisa, foi relatada uma série de cinco casos de indivíduos com TOC refratário e com comorbidades psiquiátricas submetidos à ECT. Neste agrupamento de pacientes, quatro foram indicados para a realização de ECT, devido à presença de depressão com ideação suicida, e um

deles devido ao quadro de mania. Após ao menos seis sessões de ECT, quatro obtiveram remissão parcial ou total dos sintomas depressivos ou maniformes. No entanto, nenhum deles apresentou melhora dos sintomas obsessivos-compulsivos, inclusive havendo dois pacientes que apresentaram piora dos sintomas, tendo um deles interrompido as sessões por este motivo. (LINS-MARTINS et al., 2015).

A revisão sobre técnicas neuromodulatórias no TOC de Dell'Osso e colaboradores (2005) aborda novamente o principal questionamento da ECT neste transtorno. Apesar da utilização de novos parâmetros, com o reposicionamento de eletrodos (unilateral e bifrontal) e os devidos cuidados anestésicos, a eficácia da ECT no TOC ainda não foi provada porque não existem estudos controlados-randomizados. Outro artigo de revisão de neuromodulação, porém mais atual, mostrou o resultado de doze estudos de ECT no TOC. Novamente, essa expôs uma literatura baseada em relatos de casos e estudos abertos com protocolos variados e concluiu-se que, na maioria desses, o TOC era comórbido a outros transtornos mentais, como o TAB e os transtornos psicóticos. Foram necessárias sessões de ECT de manutenção que variaram de seis a vinte e quatro meses, pois os efeitos na remissão dos sintomas obsessivos-compulsivos foram de curta duração. (BAIS; FIGEE; DENYS, 2014),

Portanto, a única revisão sistemática disponível, até o momento na literatura a respeito do tema, foi realizada por Fontenelle e colaboradores (2015). Selecionou-se ao todo 50 artigos incluindo: um estudo quase-randomizado, um estudo de caso-controle, um de coorte, vinte e dois relatos de série de casos e vinte e cinco relatos de caso. Novamente, nenhum estudo randomizado-controlado foi encontrado. Outro achado importante foi o fato de que apenas 7% dos estudos revelaram o resultado do YBOCS, corroborando para a falta de instrumentos convincentes na avaliação de eficácia da ECT no TOC. Dentre os resultados desta revisão, foi alarmante o fato de que em um total de noventa e três pacientes, apenas 52% haviam sido tratados com IRSs e destes, somente nove receberam doses apropriadas e por tempo adequado (pelo menos doze semanas). Dos estudos que forneceram dados individuais dos pacientes, tendo esses contabilizado cinquenta e sete indivíduos, pode-se inferir que a maioria apresentou TOC de início tardio, não possuíam depressão e fizeram ECT com a finalidade de tratar os sintomas obsessivos-compulsivos mais graves.

1.3 ESTIMULAÇÃO MAGNÉTICA TRANSCRANIANA (EMT)

A estimulação magnética transcraniana consiste em um método de neuromodulação não-invasivo, que através da geração de um campo magnético, permeia regiões corticais e

subcorticais. O aparelho de EMT gera uma corrente elétrica que irá alcançar uma bobina situada no escalpo. Essa gera pulsos magnéticos os quais formarão correntes elétricas que despolarizarão neurônios corticais mais superficiais, a fim de que gerem corrente que possa alcançar regiões mais profundas, subcorticais (GEORGE; LISANBY; SACKEIM, 1999; GEORGE; POST, 2011). Uma vantagem em relação à ECT é a capacidade de gerar estímulos focais. A focalização da EMT é determinada pelo ângulo formado pelas "alças" da bobina, quando esse é menor que 180º, permite que as alças tangenciem mais o escalpo, aumentando a eficácia do aparelho. (ROSSI et al., 2009) O método vem sendo utilizado há cerca de 20 anos, tendo havido um aprimoramento no próprio aparelho e nos conhecimentos a respeito de sua finalidade nas doenças neurológicas, as quais afetam regiões corticais motoras, além de seus efeitos periféricos e seus avanços na psiquiatria.

A partir de um pulso único, pode-se calcular o limiar motor, normalmente pela contração periférica do polegar, o que é variável entre os indivíduos. Esse é calculado para avaliar a energia mínima necessária para gerar um estímulo em determinado paciente (GEORGE; POST, 2011). Ademais, os aparelhos mais modernos são capazes de gerar pulsos repetitivos e mais rápidos, atuando não apenas na contração motora, mas no processo de tomada de decisão e assimilação de informações com maior durabilidade (BAIS; FIGEE; DENYS, 2014). Os estudos em psiquiatria utilizam a EMT com pulsos repetitivos, chamada estimulação magnética transcranianarepetitiva (EMTR). Outra característica importante da EMTR é que o aparelho pode gerar pulsos de baixa frequência, os quais são $\leq$ 1Hz ou de alta frequência, os quais são $\geq$ 5Hz, sendo que esses geram estímulos inibitórios e excitatórios, respectivamente. (BERLIM; NEUFELD; VAN DEN EYNDE, 2013; LEFAUCHER et al., 2014).

A EMTR surgiu com a vantagem de ser um método pouco doloroso, o qual pode ser realizado sem analgesia e com o paciente acordado, o que reduz os seus riscos. Dentre os efeitos colaterais mais comuns estão a cefaleia e a dor no escalpo, sendo que a última é amenizada com o decorrer das sessões. Houve alguns relatos de perda auditiva, mas que pode ser evitada, atualmente, com o uso de protetores auriculares, tanto para os pacientes submetidos ao método, como para os profissionais que realizam o procedimento. O risco de crises convulsivas é a complicação mais grave da EMTR, porém mais comum na EMTR de alta frequência (ROSSI et al., 2009; GEORGE; POST, 2011), mas, mesmo assim, ocorre em apenas 1,4% dos casos (LEFAUCHER et al., 2014). Com mais frequência do que as crises convulsivas podem ocorrer as síncopes por resposta vasopressora, pois duram alguns segundos. Contudo, nenhum estudo reportou prejuízo cognitivo pós-estímulo (BAIS; FIGEE; DENYS, 2014).

Durante a década de 90, estudos de neurofisiologia e neuroimagem identificaram um consumo de oxigênio e glicose reduzidos no córtex pré-frontal dorsolateral (CPFDL) à esquerda de indivíduos com depressão, caracterizando uma hipoatividade desta área (PASCUAL-LEONE et al., 1996). O primeiro estudo a estimular o CPFDL à esquerda realizou a EMTR em dezessete pacientes com depressão unipolar. Ao final de cinco dias de estimulação, foi encontrada uma redução significativa na escala de depressão de Hamilton (redução do escore de 25,2 para 13,8) (PASCUAL-LEONE et al., 1996). Recentemente, uma metanálise, incluindo artigos do ano de 1995 a 2012, identificou cerca de vinte e nove estudos randomizados-controlados de pacientes com depressão que receberam EMTR de alta frequência. Então, concluíram que a EMTR de alta frequência no CPFDL à esquerda pode ser utilizado como monoterapia ou ainda como estratégia complementar à farmacoterapia ou a terapias comportamentais (BERLIM; NEUFELD; VAN DEN EYNDE, 2013).

Seguindo os parâmetros bem-sucedidos da EMTR no tratamento da depressão, os primeiros estudos do TOC também utilizaram este mesmo alvo e com o uso da EMTR de alta frequência. Greenberg e colaboradores (1997) realizaram um estudo aberto com doze pacientes que receberam estímulos de EMTR de alta frequência primeiro no CPFDL à esquerda, depois no CPFDL à direita e ainda na região occiptal, essa última não relacionada ao TOC. Como resultado, não houve mudança em relação aos sintomas obsessivos e em relação às compulsões, viu-se apenas uma redução significativa quando estimulado o CPFDL à direita e por um período de oito horas. Alonso e colaboradores (2001) realizaram o primeiro estudo controlado-randomizado de EMTR no TOC, submetendo dezoito pacientes a dezoito sessões, com estimulação ativa ou placebo no CPFDL à direita com a EMTR de baixa frequência (1Hz), porém não encontraram diferença significativa do grupo que realizou o placebo para o grupo que realizou a estimulação ativa.

Um artigo de revisão de neuromodulação no TOC constatou que em um total de cinco estudos controlados-randomizados de EMTR, que somaram cento e quarenta e um pacientes, estimulando o CPFDL, não provou superioridade do grupo ativo em relação ao placebo (SABA; MOUKHEIBER; PELISSOLO, 2015). Consequentemente, a estes resultados inconclusivos no CPFDL, outras áreas também relacionadas aos neurocircuitos do TOC começaram a ser alvo de estudos. Baseando-se nos achados de neuroimagem que mostraram hiperexcitabilidade nos circuitos orbito-frontais, levando também a um desequilíbrio de vias estriado-talâmicas (SAXENA; RAUCH, 2000), surgiu a intenção de estimular o córtex órbito-frontal (COF) e a área motora suplementar (AMS).

A região do COF à esquerda foi explorada em um estudo controlado-randomizado que utilizou a EMTR de baixa-frequência, por três semanas (cinco sessões por semana), como estratégia complementar à farmacoterapia. Encontraram, dentre as pessoas do grupo ativo, reduções no YBOCS significativas, pois oito de dezesseis pacientes obtiveram redução ≥ 25% no escore do YBOCS e quatro pessoas desse grupo de obtiveram redução ≥ 35% no YBOCS (RUFFINI et al., 2009). A partir do resultado satisfatório encontrado no artigo citado, um estudo piloto duplo-cego, controlado-randomizado foi realizado com o intuito de estimular o COF à direita. Sendo assim, incluíram dezenove pacientes que se submeteram à EMTR de baixa frequência. Logo após uma semana de estimulação, reduziu-se significativamente o YBOCS no grupo ativo comparado ao início do estudo. Todavia, esta diminuição não se manteve um mês após a estimulação (NAUCZYCIEL et al., 2014). Até o presente momento, não foram realizados novos estudos envolvendo o COF.

Em contrapartida, a AMS parece representar o alvo mais promissor nos estudos de EMTR no TOC, pois além de ser uma área de maior acessibilidade anatômica (córtex médio-frontal), desempenha a função de conectar regiões corticais aos gânglios da base (NACHEV; KENNARD; HUSAIN, 2008). O grupo de Mantovani foi pioneiro nesta prática, executando pesquisas envolvendo o tema. Em 2006, realizaram um estudo aberto com dez pacientes com o diagnóstico de TOC e Síndrome de Tourette, submetendo-os à dez sessões de estimulação da AMS com a EMTR de baixa-frequência, e perceberam uma redução da hiperexcitabilidade em hemisfério direito. Como resultado no TOC, houve reduções significativas de até 29% no YBOCS que persistiram pelos três meses seguintes de acompanhamento. Este resultado, apesar das limitações do ensaio clínico, referentes ao tamanho da amostra e a ausência de um grupo controle, impulsionou a realização de novos estudos nesta direção (MANTOVANI et al., 2006).

Ainda Mantovani e colaboradores (2008) realizaram o primeiro estudo controlado-randomizado em vinte e um pacientes com TOC resistentes à farmacoterapia, novamente na AMS. Nesse, corroboraram o achado do estudo aberto, de redução da hiperxcitabilidade cortical. Encontraram uma diminuição nos escores do YBOCS no grupo ativo de 32% contra 11% no grupo placebo, após quatro semanas de estimulação.Publicaram a pesquisa integralmente em 2010, quando apresentaram mais quatro semanas de estimulação (totalizando oito semanas de acompanhamento), na qual realizaram o estímulo real nos pacientes que faziam parte do grupo placebo, dando continuidade ao estímulo naqueles que já faziam parte do grupo ativo. Ao final do estudo, o grupo que realizou o estímulo real apenas nas últimas quatro semanas não obteve redução significativa no escore do YBOCS. Entretanto, os pacientes que

fizeram parte do grupo ativo por oito semanas, mantiveram uma melhora clínica dos sintomas obsessivos-compulsivos, porém sem significância estatística (MANTOVANI et al., 2010).

Portanto, pode-se considerar que a ciência tem encontrado resultados mais promissores da EMTR no TOC com o uso da estimulação de baixa potência na AMS. No entanto, os estudos controlados-randomizados realizados até o momento demonstram um baixo poder estatístico, provavelmente, por apresentarem uma amostra insatisfatória. Em 2013, foi realizada uma metanálise incluindo dez estudos controlados-randomizados que abordaram os três alvos já mencionados: CPFDL, COF e AMS. Todavia, não houve significância estatística para determinar se a EMTR é eficaz no TOC. Chegaram à conclusão de que os protocolos ainda são muito heterogêneos e possuem uma amostra pequena (BERLIM; NEUFELD; VAN DEN EYNDE, 2013). Outro desafio é a realização de um grupo placebo adequado, pois com frequência os pacientes identificavam que estavam realizando o procedimento placebo. Apesar disso, mesmo a curto prazo, há uma tendência favorável ao uso da EMTR de baixa-frequência na AMS. Estudos utilizando a EMTR como método complementar à farmacoterapia e às terapias comportamentais já estão sendo feitos. (ZHONG-RUI MA; LI-JUN SHI, 2014).

1.4 ESTIMULAÇÃO TRANSCRANIANA POR CORRENTE CONTÍNUA (ETCC)

O estudo de correntes elétricas para geração de excitabilidade cortical começou a ser testado em modelos animais nas décadas de 50 e 60. A partir deles, foi possível provar que uma corrente de baixa intensidade pode gerar alteração no potencial de membrana celular (PAULUS; ANTAL; NITSCHE, 2016). Na década de 70, essa corrente também foi aplicada em humanos, com a expectativa de modulação do afeto, sintomas cognitivos e, assim, poder ser utilizada na prática clínica (NITSCHE et al., 2003). No entanto, em seguida, o crescimento da indústria de psicofármacos promoveu uma desaceleração deste processo, pelos resultados promissores que a ciência aguardava com o uso de psicotrópicos. Apenas nos últimos dezesseis anos, foi provado que o uso da ETCC em humanos promove excitabilidade neuronal que pode perdurar por até 1 hora após a estimulação (NITSCHE; PAULUS, 2000).

A ETCC consiste na geração de um campo elétrico a partir de uma corrente de fraca intensidade, em que apenas 50% dessa permeia o escalpo (NITSCHE et al., 2008). Ao atingir o córtex, a corrente circula entre os pólos positivo (ânodo) e negativo (cátodo) gerando um campo elétrico. Na dependência de canais iônicos, provoca alterações no potencial de membrana, promovendo despolarização ou hiperpolarização celular. Na fase anódica, ocorre despolarização da membrana celular e com isso hiperexcitabilidade neuronal. Na fase catódica,

há hiperpolarização das membranas celulares e, consequentemente, uma redução da atividade neuronal (NITSCHE; PAULUS, 2000). Portanto, os dois eletrodos de polaridades opostas (ânodo x cátodo) são posicionados no escalpo de acordo com o efeito neuromodulatório desejado. O eletrodo ativo é necessariamente colocado no córtex, mas o eletrodo de referência pode ser posicionado também em região extra cefálica (TORTELLA et al., 2015). O tamanho dos eletrodos varia de $3cm^2$ a $100cm^2$ (DA SILVA et al., 2011), porém convencionalmente, a maioria das montagens utiliza o eletrodo de $35cm^2$ (NITSCHE; PAULUS, 2000).

O funcionamento adequado da ETCC também depende da intensidade da corrente, que varia entre 0,5 mA e 2mA, e do tempo de duração do estímulo com mínimo de cinco minutos e máximo de quarenta minutos (TORTELLA et al., 2015). Aumentando a duração do estímulo de nove para treze minutos, espera-se que os efeitos na excitabilidade neuronal do córtex motor primário prolonguem-se de meia hora para até noventa minutos (NITSCHE; PAULUS, 2001). Ou seja, quanto maior for o tempo de estimulação, mais duradouro serão os efeitos, tanto com a estimulação anódica como catódica (NITSCHE et al.,2008). Além disso, Boggio e colaboradores (2007) corroboraram o achado de estudos anteriores de que a ETCC, quando aplicada em dias consecutivos, traz benefícios ao funcionamento motor e também aos comportamentais, sendo eficaz na reabilitação de pacientes pós-acidente vascular encefálico.

Além de ser um método de neuroestimulação não-invasivo, as suas vantagens em relação à EMTR são o fato de ser um procedimento financeiramente mais econômico, o equipamento ser portátil e de simples montagem, seguro e com efeitos adversos transitórios, de intensidade leve a moderada. Além disso, o aparelho de ETCC pode ser programado para gerar um estímulo placebo, isto é, criar uma corrente com duração de alguns segundos, permitindo realizar um protocolo de estudo controlado-randomizado, com mais facilidade e confiabilidade (NITSCHE et al., 2008). A princípio, o maior desafio do seu uso é a baixa capacidade de focalização, que se manifesta em duas situações: (1) o fato de a corrente agir nas regiões adjacentes a que se deseja estimular e (2) o fato de não ser possível garantir que o eletrodo de referência não provoque a estimulação da região onde foi posicionado quando também é colocado no córtex. Na tentativa de aprimorar a focalização, tem sido proposta a montagem monocefálica, ou aumento de tamanho do eletrodo de referência e/ou a redução do tamanho do eletrodo ativo (NITSCHE et al., 2007, 2008).

Diversos estudos em neurologia e psiquiatria trazem resultados promissores em relação ao uso da ETCC. Análises de revisão recentes relataram o uso da ETCC em dor crônica, zumbido e reabilitação pós-AVC (KUO; PAULUS; NITSCHE, 2013; TORTELLA et al., 2015), em relação à psiquiatria, a maior aplicabilidade tem sido feita na depressão maior, talvez

pelos resultados positivos, e sua aprovação para uso na clínica com a EMTR. Na revisão de Kekic e colaboradores (2016), foram encontrados trinta estudos, dentre eles, os controlados-randomizados, e estudos abertos em depressão maior unipolar e bipolar. Identificou-se que o resultado mais favorável foi a estimulação anódica no CPFDL à esquerda e catódica em região contralateral ou intra/extra cefálica. Em relação aos outros transtornos mentais, há evidências de que o ânodo no CPFDL à esquerda pode melhorar os sintomas negativos da esquizofrenia e que ambos os estímulos, catódico e anódico, no CPFDL, têm a possibilidade de reduzir a fissura na maioria dos transtornos de abuso de substâncias (KUO; PAULUS; NITSCHE, 2013).

Diferentemente dos estudos de ETCC na depressão maior, os que envolvem a eficácia deste método no TOC ainda são escassos e há muitos questionamentos a respeito do protocolo a ser seguido. Há dúvidas quanto ao alvo a ser estimulado, posicionamento dos eletrodos e número de sessões. O primeiro estudo documentado (VOLPATO et al., 2013) foi um relato de caso que comparou o resultado da estimulação catódica da ETCC no CPFDL à esquerda com a EMTR de baixa frequência na mesma região. Foram duas semanas de estimulação real (total de dez sessões), com ETCC, e após uma semana mais 10 sessões com placebo, usando também a ETCC. O mesmo foi feito em relação à EMTR, porém os resultados dos YBOCS em relação às estimulações reais e placebo não mostraram diferença significativa. Notou-se apenas uma melhora dos sintomas depressivos e ansiosos, o que, no entanto, pode ser atribuído a um efeito placebo.

Baseando-se nos resultados mais promissores da EMTR, os estudos de ETCC subsequentes se propuseram a estimular a AMS e o COF. Foram encontrados na literatura apenas outros cinco artigos, sendo quatro relatos de caso e uma série de casos, totalizando treze pacientes com TOC que foram submetidos à ETCC. No estudo de Narayanaswamy e colaboradores (2014) são descritos dois relatos de casos de pacientes que foram submetidos à ETCC, com ânodo na região pré-AMS/AMS à esquerda e o cátodo no COF à direita. Aconteceram dez sessões de estimulação, com vinte minutos de duração, sendo duas sessões por dia, separadas por três horas de intervalo. Encontrou-se redução no escore de YBOCS maior que 35% nos dois pacientes ao final dos estímulos. Em um dos indivíduos, esse resultado persistiu por um mês e no outro por dois meses. Esse mesmo grupo de pesquisadores apresentou outro relato de caso utilizando a mesma montagem de eletrodos, em que um paciente realizou sessões de ETCC intermitentes e com resultado bem-sucedido nas duas ocasiões, com redução de até 69,5% na pontuação de YBOCS (HAZARI et al., 2016).

O estudo de Mondino e colaboradores (2015) traz um relato de caso no qual o cátodo, medindo 35 cm^2, foi colocado no COF à esquerda e o ânodo medindo 100cm^2, na região

occiptal, para que o estímulo priorizado fosse inibitório no COF. Assim, executaram dez sessões de ETCC, sendo que a paciente fazia uso regular há pelo menos três meses de um ISRS associado a um antipsicótico e um estabilizador do humor em doses plenas. Foram realizados dois YBOCS no início do estudo, um logo após o término das dez sessões e outro um mês após. No YBOCS pré-ETCC, ela possuía uma pontuação de 36/40, contudo o YBOCS realizado imediatamente depois não mostrou benefício. O YBOCS após um mês mostrou redução no escore de 26%. Foi escolhido o COF à esquerda porque dois trabalhos com EMTR mostraram benefício com a estimulação desta área (RUFFINI et al., 2009; NAUCZICYEL et al., 2014). Ainda estimulando o COF, um estudo aberto com oito pacientes submetidos à dez sessões de ETCC, posicionou o cátodo de 35cm^2 no COF à esquerda e o ânodo de 35cm^2 no cerebelo (BATION et al., 2016). Realizou-se o YBOCS antes, logo após as dez sessões, após um mês s e após três meses. Logo após a ETCC, houve uma redução de 26,4% no YBOCS médio. Após três meses, cinco pacientes mostraram redução de 25% no YBOCS, mas apenas três dos oito apresentaram redução de 35% no escore de YBOCS.

Utilizando uma montagem monocefálica, foi apresentado por D'Urso e colaboradores (2015) um relato de caso de uma mulher de trinta e três anos que foi submetida à vinte sessões de ETCC, com duração de vinte minutos cada. Nas dez primeiras sessões, foi colocado o ânodo na AMS e o cátodo extra cefálico no deltoide à direita. O ânodo na AMS levou a um aumento do YBOCS de trinta e quatro pontos no início da estimulação para trinta e oito após a ETCC. Por isso, nas dez sessões seguintes fez-se a montagem invertida com cátodo na AMS, e, após as últimas dez sessões, houve uma redução no escore do YBOCS para vinte e quatro pontos. A partir destes estudos disponíveis na literatura, percebe-se a necessidade de realização de ensaios clínicos controlados-randomizados que possam trazer mais esclarecimentos em relação a melhor montagem e escolha de estimulação, se excitatória ou inibitória, na AMS. Há ainda uma discussão conceitual a respeito do papel da hiperativação desta área, se primária ou compensatória, o que pode influenciar nas escolhas pela melhor montagem de ETCC.

2. JUSTIFICATIVA

A escolha do tema "Um Estudo sobre a Neuromodulação no Transtorno Obsessivo-Compulsivo" surgiu do interesse em explorar os métodos neuromodulatórios de maior relevância nesse transtorno, uma vez que o TOC é uma enfermidade consideravelmente prevalente e com prognóstico ainda desfavorável diante de uma resposta pouca satisfatória aos

tratamentos convencionais. A partir do meu ingresso no ambulatório de Transtorno Obsessivo-Compulsivo do IPUB/UFRJ, começamos a observar que alguns pacientes pouco respondedores ao tratamento farmacológico haviam realizado ECT. Buscando referências na literatura a respeito do uso da ECT para o tratamento do TOC, constatou-se que a mesma é inconclusiva e que não existiam trabalhos mais consistentes como revisões sistemáticas ou ensaios clínicos controlados-randomizados. Dessa forma, surgiu a oportunidade de explorar este campo e também estudar os outros métodos de neuroestimulação. Foram desenvolvidos, ao longo de dois, anos quatro artigos que serão apresentados a seguir.

O primeiro artigo, "Eletroconvulsive Therapy for Obsessive-Compulsive Disorder: a Systematic Review" é uma revisão sistemática de eletroconvulsoterapia no TOC que incluiu cinquenta artigos, sendo a maioria relatos de caso para avaliar as indicações, perfis dos pacientes e eficácia do método. O segundo artigo, "Eletroconvulsive Therapy in Obsessive-Compulsive Disorder: A Chart Reviewand Evaluation of its Potential Therapeutic Effects" é uma série de casos que traz o relato de caso de cinco pacientes do ambulatório de TOC do IPUB/UFRJ que realizaram ECT. Revisa as indicações, comorbidades, resposta clínica, dentre outros aspectos.

O terceiro artigo intitulado: "Prevalenceand Correlates of Electroconvulsive Therapy Delivery in Out patients with Obsessive-Compulsive Disorder" é um estudo que fez a análise de um banco de dados de mil e um pacientes com TOC de sete centros especializados diferentes, e comparou dentre eles aqueles que realizaram a ECT com os que não passaram por esse processo, avaliando perfil sociodemográfico, comorbidades, gravidade do TOC. Os seus achados corroboram alguns aspectos presentes nos outros dois artigos já citados. O quarto artigo "An Interim Analysisof a Double-Blind Sham-Controlled Study on the Acute Effects of Transcranial Direct Current Stimulationin Obsessive-Compulsive Disorder" representa os resultados preliminares de um ensaio clínico controlado quasi- randomizado duplo-cego que estamos realizando, utilizando a ETCC em pacientes do ambulatório de TOC do IPUB/UFRJ.

3. ARTIGOS DA DISSERTAÇÃO

3.1 PRIMEIRO ARTIGO

“Eletroconvulsive Therapy for Obsessive-CompulsiveDisorder: A Systematic Review”
Publicação: *Journal Clinical Psychiatry*, 76:7, July 2015

Review Article

Electroconvulsive Therapy for Obsessive-Compulsive Disorder: A Systematic Review

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ABSTRACT

Objective: Surgical therapies for treatment-refractory obsessive-compulsive disorder (OCD), such as deep brain stimulation or psychosurgery, remain unattainable for many patients. Despite the long-held view that electroconvulsive therapy (ECT) is an ineffective treatment for OCD, there is no systematic review to support or refute this claim, which is the basis of the current review.

Data Sources: A systematic search of MEDLINE, Web of Science, Scopus, and LILACS databases was conducted on December 22, 2013, using the terms *obsessive-compulsive disorder* and *electroconvulsive therapy*. Reference lists, specific journals, and clinical trial registries were also scrutinized. No date or language limitation was imposed on the search.

Study Selection: After irrelevant and redundant records from the 500 identified titles were excluded, the 50 articles reporting the acute treatment effects of ECT in OCD and related constructs (involving a total of 279 patients) were analyzed for this study.

Data Extraction: The relevant sociodemographic, clinical, and outcome data of individual cases were extracted. Data from individual cases were used to compare the characteristics of responders versus nonresponders to ECT.

Results: Most selected records were case reports/series; there were no randomized controlled trials. A positive response was reported in 60.4% of the 265 cases in which individual responses to ECT were available. ECT responders exhibited a significantly later onset of OCD symptoms ($P = .003$), were more frequently nondepressed ($P = .009$), more commonly reported being treated with ECT for severe OCD ($P = .01$), and received a fewer number of ECT sessions ($P = .03$). ECT responders were also less frequently previously treated with adequate trials of serotonin reuptake inhibitors ($P = .05$) and cognitive-behavioral therapy ($P = .005$).

Conclusions: Although 60% of the reported cases reviewed exhibited some form of a positive response to ECT, it cannot be stated that this provides evidence that ECT is indeed effective for OCD.

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Obsessive-compulsive disorder (OCD) is a frequent and debilitating condition[1] whose symptoms tend to group into 4 different thematic clusters: contamination/washing, taboo thoughts/checking, symmetry/ordering, and hoarding/collecting themes.[2] Available treatments for OCD include serotonin reuptake inhibitors (SRIs) administered in maximum tolerated doses for a sufficient period of time (minimum of 12 weeks)[3] and/or cognitive-behavioral therapy (CBT) in the form of exposure and response prevention.[4] In general, 40% to 60% of OCD patients show what have been considered favorable responses to these forms of treatment,[5] usually defined as at least 25% decrease in the initial score on the Yale-Brown Obsessive-Compulsive Scale (YBOCS) plus a Clinical Global Impressions-Improvement scale (CGI-I) score of 1 or 2.[6]

Adequate management of OCD patients who do not respond to an initial trial with selective SRI and/or CBT involves the sequential administration of a different SRI (including clomipramine) that, if needed, can be augmented by CBT or dopamine blockers for those who were not exposed to it.[7,8] However, experts have suggested that up to 10% of treatment-seeking OCD patients will show inadequate response to these strategies.[9] Modern neurosurgical therapies for treatment-refractory OCD, such as deep brain stimulation[10] or limbic system surgery,[11] remain unfeasible for many patients due to costs and/or access and have not been fully evaluated in regard to efficacy and safety. Theoretically, it may be that treatment-refractory OCD patients could be saved from more invasive procedures if a trial with electroconvulsive therapy (ECT) were undertaken.[12] However, it has been argued that the evidence for the efficacy of ECT in OCD remains sparse.[13–15]

Some ECT experts are more optimistic about the occasional utility of ECT in treatment-refractory OCD,[12] although this mode of treatment is not mentioned in the official algorithms developed by OCD specialists.[16] Historical reasons, lack of good quality data, and personal experiences may be at the core of this therapeutic inconsistency. For instance, some authors have suggested that defining and characterizing a subset of potential ECT responders should be subject to a definitive controlled study,[13] while others have argued that the burden of experience does not suggest that controlled comparisons would be helpful.[17] Indeed, despite many disparate opinions regarding the efficacy of ECT for OCD, we are not aware of any study that reviewed its efficacy in a systematic way.

In this review, we analyzed studies reporting the socio-demographic, clinical, and outcome features of OCD patients treated with ECT as described in the medical literature. Our objectives were 2-fold: (1) to assess the effectiveness and determine the rates of response to ECT among OCD patients and (2) to identify features related to a positive treatment response of OCD to ECT.

Clinical Points

- Although it cannot be unequivocally stated that ECT is effective for OCD, 60% of the ECT-treated OCD cases exhibited some positive response.
- Our findings suggest that ECT responders had later onset of OCD symptoms, were more frequently nondepressed and treated for severe OCD, and received fewer ECT sessions.
- Clinicians using ECT in OCD, however, have frequently ignored effective doses and duration of SRIs and cognitive-behavioral therapy and may have prescribed ECT prematurely in a number of cases.

METHOD

Criteria for Considering Studies for This Review

We searched for randomized trials, observational studies, retrospective investigations, case series, and single case reports of ECT use in OCD (*DSM* or *ICD* diagnosed) and corresponding constructs (eg, obsessional neurosis, obsessional psychoneurosis, obsessional states, and psychasthenia). Studies in which OCD was comorbid to other psychiatric conditions were also included as long as the specific effect of ECT on OCD was detailed. Studies focusing on other OCD spectrum conditions (eg, body dysmorphic disorder, Tourette syndrome, self-mutilating behaviors), medication-induced OCD (eg, OCD due to clozapine), or OCD resulting from neurodegenerative conditions (eg, Pick disease, progressive supranuclear palsy, neuroacanthocytosis) were preliminarily excluded from our analysis.

The intervention of interest in this review was unilateral or bilateral ECT. Studies assessing the acute treatment effects of ECT in OCD were included regardless of concomitant reports on the effectiveness of maintenance ECT. We also included studies that maintained other forms of treatments during ECT (ie, SRI) or that included treatments starting simultaneously with ECT. The primary outcome measure was the authors' categorical report of significant reduction in the severity of obsessive-compulsive symptoms as a result of ECT. However, we also assessed whether patients were evaluated pretreatment and posttreatment with the Yale-Brown Obsessive Compulsive Scale (YBOCS).[18,19]

Search Methods for Identification of Studies

A systematic search of MEDLINE, Web of Science, Scopus, and LILACS databases was conducted on December 22, 2013, using the terms *obsessive-compulsive disorder* and *electroconvulsive therapy* as MeSH major topics (in MEDLINE); topics (in Web of Science); article titles, abstracts, and keywords (on Scopus); and health sciences descriptors (in LILACS). Reference lists of selected articles, *Journal of ECT*, *Convulsive Therapy*, *Brain Stimulation*, and relevant books[20–26] were also hand-searched and cross-referenced for any additional studies that could be included. The first author also searched the Cochrane Library and clinical trial registries for ongoing or completed trials (ClinicalTrials.gov and World Health Organization International Clinical Trials Registry Platform). No date limit or language restrictions were applied. Editorials, commentaries, reviews, lectures, and letters not containing original data were excluded.

Data Collection and Analysis

Selection of studies. All citations identified as potentially relevant by the literature search were closely inspected, and all redundant records identified through different databases searched were excluded from the review. Relevant articles were identified and screened for thematic suitability. This was followed by an assessment of eligibility according to inclusion and exclusion criteria. If this information was unclear, an attempt was made to contact the corresponding author(s). Discrepancies regarding inclusion and exclusion of the studies were resolved by consensus within the team of authors.

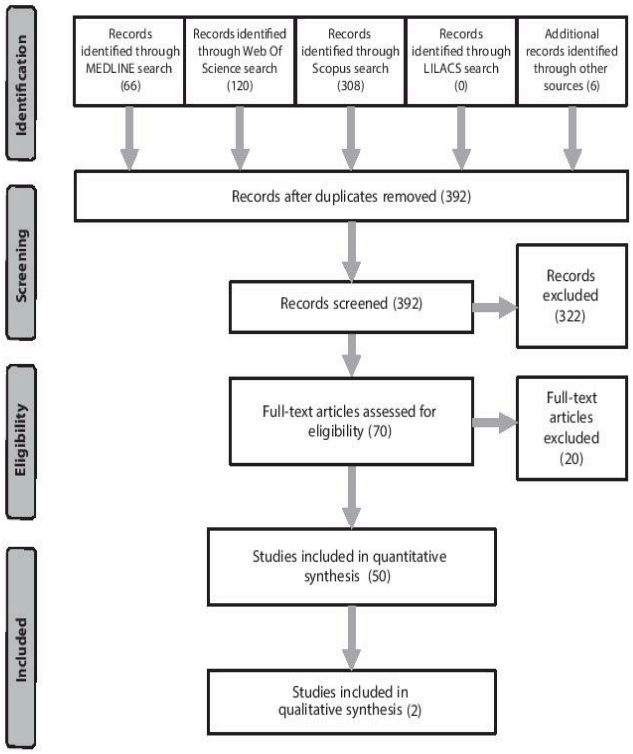
Analysis of individual studies. When appropriate, studies were assessed for quality following the Cochrane criteria[27] including (1) random sequence generation; (2) allocation concealment; (3) blinding of participants, personnel, and outcome assessors; (4) selective reporting; and (5) incomplete outcome data. We specifically described only studies with more than 1 treatment arm. We also assessed the likelihood of any publication bias by comparing the rates of positive treatment response between single case reports and case series versus studies including more than 1 treatment arm.

Analysis of individual cases. If studies were selected for inclusion, we collected and entered the individual data into an SPSS database (SPSS Inc, Chicago, Illinois), including demographic and clinical factors (ie, age, gender, age at OCD onset, OCD symptom dimensions, pretreatment YBOCS severity scores, course of illness, comorbidity patterns, and reasons for ECT administration), treatment history (ie, whether there was history of adequate treatment with an SRI in terms of dose and minimum duration and/or of CBT), ECT parameters (ie, whether ECT was bilateral or unilateral, the total number of ECT sessions, and the number of ECT sessions per week), and treatment response (ie, posttreatment YBOCS severity scores, the presence of response of OCD to ECT according to the author's opinion, the presence of response of major depression to ECT according to the author's opinion, duration of follow-up, and relapse or worsening of OCD).

A priori analyses of ECT responders versus nonresponders were planned based on the following variables:

1. age
2. gender
3. age at OCD onset
4. OCD symptom dimensions
5. course of illness
6. comorbidity patterns
7. reasons for ECT administration
8. previous exposure to an SRI

Figure 1. Description of Identification, Screening, Eligibility, and Inclusion of Studies in This Review According to the PRISMA Recommendations



9. previous exposure to an adequate trial with SRI in terms of either maximum dose tolerated or minimum duration of 12 weeks
10. previous exposure to CBT
11. bilateral or unilateral ECT
12. total number of ECT sessions
13. number of ECT sessions per week

RESULTS

Study Selection

The literature search identified 500 potential titles. After all redundant records were identified and removed, a total of 392 articles remained. These remaining articles were screened for thematic suitability by checking titles and abstracts, which generated 70 articles assessed as being suitable for eligibility based on the specific criteria. A total of 20 articles were excluded on the basis that they (1) failed to adequately describe the responses of OCD to ECT[28–32]; (2) reported the ECT-related response of depression rather than OCD[33]; (3) described responses of OCD symptoms to ECT in the context of neurodegenerative conditions,[34–38] drug-induced OCD,[39] other OCD spectrum disorders,[40,41] non-OCD spectrum psychiatric disorders,[42] or unclear diagnoses[43]; (4) reported cases already described in the selected literature[44]; or (5) merely reviewed the literature or provided an opinion concerning the use of ECT or other neurostimulatory approaches in OCD.[45–47] For a description of the identification, screening, eligibility, and inclusion of studies according to PRISMA recommendations,[48] see Figure 1.

Analyses of Individual Studies

As no randomized controlled trial on the efficacy of ECT in OCD was found, we focused our systematic review on 1 non-randomized or quasi-randomized study,[49] 1 case-control study,[50] 1 cohort study,[51] 22 case series, and 25 single case reports (see Table 1 for a description of different aspects of each selected study). As we have noted, only 2 studies included more than 1 treatment group, at least 1 describing response to ECT.[49,51] Although the study by Ferrão et al[50] compared 2 groups (treatment-refractory vs non–treatment-refractory OCD patients) and provided data for individual case analyses, we decided not to describe it since it was not focused on the response to ECT.

The first study[49] was presented as a poster at a European conference meeting. We considered it a nonrandomized trial, as no clear information on allocation of study subjects to each therapeutic approach was provided. In this study, a total of 66 inpatients with OCD were assigned to ECT (17 patients) versus SRI or "cyclic" antidepressant (49 patients) treatment arms. Efficacy of ECT was assessed with YBOCS, Hamilton Depression Rating Scale (HDRS), and CGI. According to the authors, CGI scores showed marked improvement in 60% of both groups. However, patients treated with ECT (average = 7.9 sessions/patient) showed more days of hospitalization (37.7 vs 30.1 days).

While this study suggests that ECT is as effective as an antidepressant (ie, improved CGI score was noted) in inpatients with severe OCD, a number of gaps make it difficult to judge the methodological qualities of the study. For instance, the study by Garrido[49] did not include information concerning the scores on the YBOCS and HDRS. Also, other than similar age and gender, there was too little information on possible differences between the 2 groups (ECT vs antidepressants) in terms of baseline characteristics. Therefore, it was not clear how interventions were allocated to participants and if there was allocation concealment. We were also unable to exclude systematic differences in the care that was provided (ie, duration of treatment was not available for each treatment arm and it is unclear when endpoint analyses were done).

In addition, the study by Garrido[49] was hampered by the fact that no sham ECT was mentioned in the antidepressant-treated group or placebo pill in the ECT group, a limitation that, together with the above mentioned differences in the

Table 1. List of Studies Included in the Present Systematic Review

Study First Author and Year	ECT Patients, N	Design	Principal Indication for ECT	Response Rate, %
Lins-Martins, 2014[52]	5	Case series	MDE (4 patients) and mania/agitation (1 patient)	0
Bülbül, 2013[53]	1	Case report	MDE	100
Sheehan, 2013[54]	2	Case series	Treatment resistance	0
Grover, 2013[55]	1	Case report	Treatment resistance	0
D'Urso, 2012[56]	1	Case report	Catatonia	100
Raveendranathan, 2012[57]	1	Case report	Treatment resistance	100
Makhinson, 2012[58]	1	Case report	Catatonia	100
Riestra, 2011[59]	1	Case report	Treatment resistance	0
Loi, 2010[60]	1	Case report	Severe OCD	100
Tomruk, 2010[61]	2	Case series	Treatment resistance (1 patient) and severe OCD (1 patient)	100
Hanisch, 2009[62]	1	Case report	Severe OCD	100
Nilsson, 2009[63]	1	Case report	Severe OCD	100
Talaei, 2009[64]	1	Case report	Treatment resistance	0
Fisher, 2008[65]	1	Case report	Treatment resistance	100
Schindler, 2008[66]	1	Case report	Treatment resistance	0
García Valls, 2007[67]	1	Case report	Mania/agitation	100
Ferrão, 2006[50]	4	Case-control study	Treatment resistance	0
Chaves, 2005[68]	1	Case report	Mania/agitation	100
Strassnig, 2004[69]	1	Case report	Severe OCD	100
Thomas, 2003[70]	1	Case report	MDE	100
Polosan, 2003[71]	2	Case series	Treatment resistance	0
Fukish, 2003[72]	1	Case report	Severe OCD	100
Chung, 2001[73]	1	Case report	Treatment resistance	0
Ganesan, 2001[74]	1	Case report	Unclear	100
Swartz, 1999[75]	3	Case series	Severe OCD	100
Shusta, 1999[76]	1	Case report	Unclear	0
Garrido, 1998,[49]	17	NRT	Unclear	58.8
Lavin, 1996[77]	1	Case report	Treatment resistance	100
Filer, 1996[78]	1	Case report	MDE	100
Wohlfahrt, 1996[79]	1	Case report	Drug side effects	100
Beale, 1995[12]	3	Case series	Treatment resistance	100
Casey, 1994[80]	1	Case report	MDE	100
Maletzky, 1994[81]	32	Case series	Treatment resistance	At least 56.2
Husain, 1993[82]	1	Case report	Treatment resistance	100
Sichel, 1993[83]	1	Case report	MDE	0
Schott, 1992[84]	1	Case report	Treatment resistance	0
Soyka, 1991[85]	1	Case report	Treatment resistance	100
Warneke, 1989[86]	2	Case series	Treatment resistance	0.0
Khanna, 1988[87]	9	Case series	Treatment resistance	77.8
Mellman, 1984[88]	1	Case report	Previous response	100
Dubois, 1984[51]	19	Cohort study	Unclear	78.9
Walter, 1972[89]	80	Case series	Treatment resistance	43.8
Grimshaw, 1965[90]	32	Case series	Unclear	50
Korson, 1949[91]	1	Case report	Severe OCD	100
Bini, 1947[92]	4	Case series	Unclear	75
Hamilton, 1947[93]	9	Case series	Unclear	88.9
Milligan, 1946[94]	11	Case series	Unclear	100
Kerman, 1945[95]	1	Case report	Unclear	100
Moriarty, 1943[96]	5	Case series	Unclear	100
Smith, 1943[97]	7	Case series	Unclear	14.3

Abbreviations: ECT = electroconvulsive therapy, MDE = major depressive episode; NRT = nonrandomized trial, OCD = obsessive-compulsive disorder.

treatment provided, has the potential to affect blinding. Although outcomes were determined similarly (with CGI) in both treatment groups, the already mentioned lack of information on baseline and endpoint YBOCS and HDRS scores does not exclude the possibility of selective reporting of outcomes. Finally, no information on dropout rates was provided, which further limits the generalizability of the treatment effects.

The second investigation including a comparative group was a cohort study involving heterogeneous intervention strategies in each treatment arm.[51] More specifically, it included 14 patients treated with oral antidepressants (8 clomipramine, 4 chlorpromazine, 1 phenelzine, and 1 sulpiride), 10 patients treated with intravenous followed by oral antidepressants (9 clomipramine and 1 amitriptyline), 9 patients treated with intravenous plus oral antidepressants (specific drugs not mentioned) plus ECT, and 10 patients treated with oral antidepressants (9 clomipramine—associated with amitriptyline in 1 and imipramine in another—and isolated amitriptyline in another) plus ECT. At the end of 3 months of treatment, 12 (85.7%), 6 (60%), 7 (78%), and 6 (60%) patients, respectively, were described as "cured." Perhaps because of methodological limitations inherent to their approach, these authors did not compare rates of response between the groups or discuss the superiority of any treatment dispensed. Instead, they described the improvement rates for the whole group as an average of 69.7%.

Predictably, the therapeutic flexibility reported in this cohort study by Dubois[51] introduced systematic differences in the treatment provided, wherein patients received different combinations of therapeutic strategies (ie, oral antidepressants, intravenous antidepressants, hypnotics, and ECT) according to different clinical demands. In this study, treatment arms were defined a posteriori, thus hindering any attempt to perform reliable comparisons of response rates between groups. Apparently, in this study, patients whose illness was particularly severe were more likely to be treated with ECT and intravenous antidepressants, although this was not explicitly mentioned.

In terms of publication bias, there was no difference in positive response to ECT described in case reports and case series (60.0%) vs studies with more than 1 treatment arm (62.5%; $\chi^2_1 = 0.09$, $P = .76$). However, patients showing positive responses to ECT were more commonly described in recent studies (66.3%) as compared to older ones, albeit without statistical significance (57.5%; $\chi^2_1 = 1.84$, $P = .17$). Finally, we found an increased representation of case report descriptions of patients from more recent studies (ie, those published after 1990; 91.7%) compared to older ones (8.3%; $\chi^2_1 = 37.2$, $P < .001$).

Analyses of Individual Cases

A total of 279 OCD patients were treated with ECT: 17 in a nonrandomized or quasi-randomized trial, 19 in a cohort study, 4 in a case control study, 214 in case series, and 25 in case reports (Table 1). However, individual response rates to

ECT were available in only 265 cases. In these cases, 60.4% (n = 160) showed response to ECT according to their authors' opinion.* However, studies reporting YBOCS scores were almost negligible (ie, this information was available in only 7 cases of the total sample; 2.5%). If only cases published after the widespread availability of SRI were considered (ie, those published after 1990), the rate of treatment response was roughly comparable (ie, 66.3%). In addition, only 7.2% of the more recent cases included information on YBOCS scores. In these patients, YBOCS scores varied from 23 to 40, with a mean of 36.2 (SD = 6.3) points. The mean endpoint YBOCS score in the reported cases was 8.5 (SD = 7.9).

Information on gender was available in 106 valid cases, the slight majority of patients being female (51.9%). Age at OCD onset was accessible in 126 patients and varied from 8 to 81 y ears, with a mean (SD) of 27.1 (8.5) years. Among the valid cases, the patient's main symptom dimensions were described as taboo or forbidden thoughts (with aggressive, sexual, or religious content) and/or checking compulsions in 49 of 61 patients (80.3%), contamination thoughts and/or washing compulsions in 36 of 61 (59.0%), symmetry/ordering symptoms in 11 of 42 (26.2%), hoarding/collecting symptoms in 2 of 42 (4.8%), and other OCD symptoms (eg, somatic obsessions) in 16 of 62 (25.8%). Major depression at the time of ECT was reported in 56 of 97 cases (57.7%), nonaffective psychosis (eg, schizophrenia) in 5 of 38 (13.2%), and mania in 1 of 51 (2.0%). It was possible to determine the course of OCD in only a small minority of cases (12), which revealed that it was episodic in 66.7% (n = 8) and chronic in 33.3% of patients (n = 4).

According to the reviewed studies, "treatment-resistant" OCD was the most frequent indication for ECT, being reported in 147 (90.2%) of the 163 valid cases. However, previous exposure to CBT or to a trial with an SRI was described in only 37.6% (59/157) and 21.5% (59/275) of the cases, respectively; of note, in only 16.9% of SRI-treated patients (10/59) was there enough information to consider patients as being adequately treated, based on dose and duration of treatment. Even if one focuses on studies published after the widespread availability of SRI on the market (post-1990), the rates of SRI use remain considerably low; in these studies, only 52.7% of OCD patients (49/93) were reported as having been treated with an SRI, and, among these, only 18.4% (9/49) were described as having been treated with adequate doses of SRI for at least 12 weeks.

Besides treatment-resistant OCD, other reasons for prescription of ECT were assessed in our study. For instance, ECT was prescribed for severe OCD in 114 of 186 patients (61.3%); major depression with suicidality in 96 of 163 (58.9%); severe mania, psychosis, or agitation in 5 of 163 (3.1%); previous response to ECT or seizure in 4 of 163 (2.5%), catatonia in 3 of 163 (1.8%), and drug-related side effects in 1 of 182 (0.5%). From 90 valid cases, ECT was bilateral in 75 of 90 (83.3%), unilateral in 6 of 90 (6.7%), and alternating between unilateral and bilateral in the remaining 9 of 90 (10.0%). Total number of ECT sessions was available in 121 cases, with a mean (SD) of 9.1 (5.4) sessions per patient. Information on the weekly frequency of ECT was reported in 104 cases: it varied from 1 to 7 per week, with a mean (SD) of 3.7 (0.7) weekly sessions being employed.

Data on duration of follow-up, if any, were available in 67 cases; it varied from 1 to 24 months, with a mean (SD) of 9.9 (4.6) months. In 68 of 279 cases (24.4%), there was information on follow-up. Among these patients, 32.2% (19/59) showed relapse or worsening of OCD symptoms after ECT. The analysis of the 57 cases in which individual responses to ECT were available showed that responders displayed later onset of OCD symptoms, were more frequently nondepressed, and more commonly reported being treated with ECT for severe OCD symptoms. However, patients who responded to ECT were less frequently previously treated with adequate doses of SRI prescribed for sufficient time and less frequently provided CBT. Finally, patients who responded to ECT were treated with a lower number of ECT sessions. For detailed information on these results, see Table 2.

DISCUSSION

In this review, we were unable to find unequivocal evidence supporting the efficacy of ECT in OCD, as no randomized controlled trial (RCT) has been conducted to date. Even observational studies with comparative groups were rare. However, positive responses to ECT were reported in at least 60.4% of the total sample. Arguably, this rate of treatment response could result from the inclusion of older studies, published before the availability of more effective treatment strategies, such as SRIs and CBT and hence the inclusion of non–"treatment-resistant" patients. According to this view, focus on more recent studies would result in lower response rates to ECT. However, if only cases published after the widespread availability of SRIs are considered (ie, articles published after 1990), the rate of treatment response was roughly similar or slightly higher (ie, 66.3%).

Despite these high treatment response rates, we also found evidence that OCD patients treated with ECT have frequently received inadequate treatment prior to ECT. For instance, in just 52.7% of the most recent studies mentioned above, patients were clearly previously treated with an SRI. In addition, in only 16.9% of SRI-treated patients was enough information available on dose and duration of administration, thus suggesting that clinicians reporting ECT use in OCD have frequently ignored effective doses and duration of SRI treatment and may have prescribed ECT prematurely in a number of reported cases. This finding is particularly worrisome in the light of current doubts regarding the true efficacy of ECT in OCD. It also suggests that many patients treated effectively with ECT had more benign forms of OCD and were inaccurately labeled as "treatment resistant."

It is also worth noting that information on maintenance of gains was frequently not available, as only 24.4% of published cases were accompanied by relapses rates, with periods

*Among the 279-patient sample, information on responses to ECT was unclear in 14 of 32 patients from a single study.[81]

Table 2. Comparison Between Sociodemographic, Clinical, and Therapeutic Features of Patients With OCD Who Showed Negative vs Positive Responses to ECT[a]

Variable	Negative Response to ECT; n = up to 20[b]	Positive Response to ECT; n = up to 36[b]	Statistics
Age, mean (SD), y	38.6 (12.0)	40.00 (15.1)	$Z = -0.06$, $P = .95$
Gender			$\chi^2 = 0.4$, $df = 1$, $P = .50$
Female	9 (47.4)	21 (56.8)	
Male	10 (52.6)	16 (43.2)	
Age at OCD onset, mean (SD), y	20.6 (4.8)	34.3 (16.7)	$Z = -2.88$, $P = .003$
Predominant OCD symptoms[c]			
Taboo thoughts/checking	12 (80.0)	19 (70.4)	Fisher test, $P = .72$
Contamination/washing	5 (33.3)	14 (51.9)	$\chi^2 = 1.3$, $df = 1$, $P = .24$
Symmetry/ordering symptoms	6 (40.0)	5 (18.5)	Fisher test, $P = .16$
Hoarding/collecting symptoms	0 (0.0)	2 (7.4)	Fisher test, $P = .53$
Other OCD symptoms	4 (26.7)	11 (39.3)	$\chi^2 = 0.7$, $df = 1$, $P = .41$
Course of OCD			Fisher test, $P = .09$
Chronic	2 (100.0)	2 (20.0)	
Episodic	0 (0.0)	8 (80.0)	
Major comorbidities at time of ECT			
Major depression	12 (80.0)	12 (38.7)	$\chi^2 = 6.9$, $df = 1$, $P = .009$
Schizophrenia related disorders	1 (8.3)	4 (15.4)	Fisher test, $P = 1.0$
Mania	1 (8.3)	0 (0.0)	Fisher test, $P = .3$
Indication for ECT			
Treatment resistance	10 (62.5)	16 (61.5)	$\chi^2 = 0.004$, $df = 1$, $P = .9$
Severe OCD symptoms	2 (11.8)	15 (48.4)	$\chi^2 = 6.4$, $df = 1$, $P = .01$
Major depression with suicidality	6 (37.5)	10 (38.5)	$\chi^2 = 0.004$, $df = 1$, $P = .9$
Catatonia symptoms	0 (0.0)	3 (11.5)	Fisher test, $P = .2$
Mania, psychosis, or agitation	2 (12.5)	3 (11.5)	Fisher test, $P = 1.0$
Previous response to ECT	0 (0.0)	4 (15.4)	Fisher test, $P = .2$
Drug-related side effects	0 (0.0)	1 (3.8)	Fisher test, $P = 1.0$
Treatment history			
SRI prescribed	15 (75.0)	21 (56.8)	$\chi^2 = 1.8$, $df = 1$, $P = .17$
With adequate dose and time[d]	7 (46.7)	3 (14.3)	Fisher test, $P = .05$
Antipsychotic prescribed	14 (93.3)	20 (83.3)	Fisher test, $P = .63$
CBT	10 (83.3)	8 (33.3)	$\chi^2 = 8.0$, $df = 1$, $P = .005$
ECT-related variables			
Total no. of sessions, mean (SD)	12.4 (4.4)	10.2 (7.9)	$Z = -2.1$, $P = .03$
Frequency of weekly application, mean (SD)	2.3 (0.5)	3.1 (1.6)	$Z = -1.2$, $P = .20$
Mode of application			Fisher test, $P = .6$
Unilateral	1 (11.1)	5 (21.7)	
Bilateral	8 (88.9)	18 (78.3)	

[a]Values shown as n (%) unless otherwise noted.
[b]Data for all variables were not available in all studies.
[c]Percentages do not add up to 100 because individuals typically have more than 1 symptom dimension.
[d]With a history of being treated with adequate doses of SRI for at least 12 weeks.
Abbreviations: CBT = cognitive-behavioral therapy, ECT = electroconvulsive therapy, OCD = obsessive-compulsive disorder, SRI = serotonin reuptake inhibitor.

of follow-up that have been extremely heterogeneous. Unfortunately, deterioration in OCD symptoms was seen in more than a third of effectively treated OCD patients. While these relapse rates are somewhat lower than the 51% reported 1 year after ECT in depression,[98] they probably represent an underestimate, as information on follow-up was not available in most patients. Indeed, increased rates of relapse in ECT-treated OCD patients were already reported and suggest that, besides RCTs, studies including longer follow-up periods and treatment arms that contain relapsing prevention strategies are also needed.

Analysis of cases in which individual responses to ECT were available showed that ECT responders exhibited later onset of OCD symptoms, were more frequently nondepressed, and more commonly reported being treated with ECT for severe OCD symptoms. In fact, higher age at onset has already been associated with better responses to other forms of treatment in OCD (including SRI[99–103] and CBT[103,104]). However, severe (ie, delusional) depression has been described as a predictor of good responses to ECT,[23] an observation that is in apparent contrast to our findings. Indeed, there is evidence that depression in OCD is likely to involve different neural pathways than depression in other contexts,[105] a phenomenon that could explain its lower ability to predict treatment response. For instance, previous studies have shown that depression related to OCD is more responsive to serotonergic rather than noradrenergic drugs.[106] Finally, the fact that effective ECT was more likely to be recommended for severe, but not treatment-resistant OCD dovetails with the idea that ECT is more likely to work in noncomplicated forms of OCD.

The observation that patients who responded to ECT were less frequently previously treated with adequate trials of an SRI and less frequently provided CBT supports the earlier interpretation that ECT was more likely to treat OCD that would be otherwise treatable by conventional antiobsessional treatments, if they were prescribed. Although this finding indicates that clinicians may be misinformed about adequate treatment of OCD,[107,108] it could still be argued that ECT may be used in situations in which SRIs and/or CBT is potentially problematic or not feasible, such as in the presence of bipolar depression[109–115] associated with paralyzing fears about the consequences of exposure and response prevention sessions.[116] However, as reported above, comorbid depression was associated with resistance to ECT in OCD. Patients who were effectively treated with ECT were also submitted to a lower number of ECT sessions. Rather than suggesting that fewer ECT sessions are sufficient to treat OCD, this finding could equally reflect that patients who do not respond to ECT are treated more frequently with a greater number of ECT sessions in an attempt to overcome resistance.

Although we did not find an RCT, we detailed 2 studies reporting 2 or more treatment arms, at least 1 of which involved ECT administration, combined or not with other forms of treatment. Both have several limitations. First, the study by Garrido[49] comparing ECT to different antidepressants had incomplete information on a number of features and thus was likely to be affected by a range of methodological problems, including selection (unclear method of allocation to treatment), performance (poor

blinding to treatment), reporting (selective outcome reporting), and attrition bias (incomplete outcome data). In addition, the cohort study by Dubois[51] had limitations that are inherent to an observational design (eg, in these studies, severely ill patients may be more likely to receive multiple treatments).

Our review has its own limitations. For instance, inclusion criteria were broad, encompassing nonrandomized trials, observational studies, and, most critically, case series and single case reports. Further, by selecting studies with OCD, obsessional neurosis and, psychasthenia, we may have included individuals who, despite having overlapping conditions on a symptom level, are conceptually different. In addition, treatment response was loosely defined, based exclusively on authors' consensual personal opinions. However, restricting our review to high-quality studies, such as those involving RCT design, *DSM*-diagnosed cases, and reporting of scores measured by valid scales (such as the YBOCS), would impede or critically limit our ability to amass a reasonable number of studies and perform appropriate statistical analyses, particularly on a topic characterized by substantial missing information.

Given that OCD has been considered by some a contraindication to ECT,[17,117] that current treatment guidelines exclude ECT from their algorithms,[16] and that modern treatments for treatment-refractory OCD cases are either invasive and irreversible (neurosurgery) or expensive (deep brain stimulation),[118] we predicted that there would be overreporting of positive findings in case reports/series, as clinicians would feel stimulated to report their isolated cases of success using ECT in OCD. However, we did not find clear evidence for publication bias.

In spite of our findings, it is possible that the heterogeneity of OCD cases treated with ECT and the variation in outcomes reported by observers using its *DSM* definition may have obfuscated the potential role of ECT in OCD. For instance, since catatonia shows very high rates of response to ECT,[119] it has been suggested that some low-order repetitive behaviors[120] (such as self-injury behaviors in autism[121] and tics in Tourette syndrome[40]) can be alternate catatonic signs that may potentially predict response to ECT. Therefore, any future systematic study of ECT in OCD should investigate whether different natural history features (eg, acuteness of onset, periodicity of relapse, duration of illness), target symptoms (eg, ticlike compulsions, motor or vocal tics, self-injurious stereotypies), or associated syndromes (eg, catatonia, mania, psychosis) might, at least theoretically, predict response to ECT in OCD.

In sum, the present state of knowledge suggests that ECT has no role in the routine treatment of OCD. Although nonrandomized and cohort studies, case series, and some single case reports have suggested beneficial effects of ECT in OCD under special circumstances, these studies are limited by a lack of standardized assessment of results, history of less than optimal treatment of OCD, and poorly defined treatment resistance. In fact, cases of OCD argued to have been effectively treated with ECT (almost 60% of the sample) were probably more benign than those described as resistant according to modern criteria. Thus, our findings suggest that OCD patients labeled treatment refractory according to current criteria would be unlikely to show any response to ECT. In patients who show some response to ECT acutely, maintenance of gains is unclear at best, as most studies did not include information on treatment follow-up.

Drug names: clomipramine (Anafranil and others), clozapine (Clozaril, FazaClo, and others), imipramine (Tofranil and others), phenelzine (Nardil).

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3.2. SEGUNDO ARTIGO:

“Eletroconvulsive Therapy for Obsessive-Compulsive Disorder: A Chart Review and Evaluation of Its Potential Therapeutics Effects”.

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Electroconvulsive Therapy in Obsessive-Compulsive Disorder: A Chart Review and Evaluation of Its Potential Therapeutic Effects

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In a chart review of patients with obsessive-compulsive disorder (OCD) attending a university clinic, ECT was prescribed for five subjects (1.2%), only because of severe intervening manic (N=1) or depressive episodes (N=4). Although affective symptoms improved in four of the five patients, OCD symptoms remained unchanged (N=3) or transiently worsened (N=2).

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Obsessive-compulsive disorder (OCD) is characterized by combinations of distressful thoughts, images or urges (obsessions), and repetitive mental or motor behaviors that are performed to reduce states of emotional discomfort or according to rigid rules (compulsions).[1] Typically, the symptoms of OCD organize themselves into five thematic clusters, including 1) contamination and washing; 2) sexual and religious; 3) aggressive and checking; 4) symmetry and ordering; and 5) hoarding.[2] In the most recent edition of the DSM diagnostic system (DSM-V), OCD is at the core of a new category termed "obsessive-compulsive and related disorders," together with body dysmorphic disorder, hoarding disorder, trichotillomania, and excoriation disorder.[1]

First-line treatments of OCD include serotonin reuptake inhibitors (SRIs) and cognitive behavioral therapy involving exposure and response prevention techniques. Typically, treatment with these strategies leads to therapeutic responses in up to 60% of patients with OCD.[3] Furthermore, if partially responsive patients are treated with SRIs in combination with augmentation strategies (e.g., antipsychotics) and remain adherent to treatment on a long-term basis, as many as 90% may eventually show a beneficial response.[4] Despite these apparently favorable figures, the treatment of patients with OCD can still be challenging for several reasons, including poor treatment adherence, increased family accommodation, intolerable side effects of SRIs, lack of an appropriate response, and the development of comorbidities that can be severe and difficult to treat, such as severe depression and acute mania.

There is a pressing need to study alternative treatment strategies for patients with treatment-resistant OCD. In fact, despite the long-held perception that ECT is ineffective for OCD,[5,6] there is a handful of reports pertaining to its successful use in patients with this condition. For instance, some have advocated for ECT in an attempt to manage treatment-resistant OCD,[7] whereas others argue that a unique form of this latter condition (i.e., treatment-resistant OCD that is secondary to a primary depressive illness[8]) may be particularly responsive to ECT. Some have also suggested that ECT should be reserved for the treatment of comorbid disorders in OCD rather than the OCD itself.[9] To help shed light on this complex issue, we describe the frequency of ECT use, the reasons for its prescription, and associated outcomes in patients attending a university-based OCD clinic. It is hoped that the findings will help guide future decisions regarding the potential therapeutic use of ECT in OCD.

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METHODS

A retrospective chart-review of 420 records of patients with OCD seen in an OCD clinic in Rio de Janeiro, Brazil, during the period between 1998 and 2013 was performed. A trained clinician (N.L.M.) reviewed the medical records and extracted information concerning demographics (age and sex), OCD-related data (i.e., age at onset and OCD predominant dimensions), concomitant psychiatric diagnosis (according to the Structured Clinical Interview for DSM-IV Axis I Disorders), pre-ECT treatment features (i.e., previous adequate drug trials), and the patterns of response to ECT [i.e., primary indications for ECT, total number and frequency of ECT sessions, and response to ECT according to Clinical Global Impression (CGI)]. No charts were excluded on the basis of lack of sufficient information. This research protocol was approved by our local institutional review board.

RESULTS

ECT was prescribed for only five patients (1.2%) across the entire sample (N=420). In these cases, ECT was used primarily for intervening mood disorders, including acute mania (one patient) and major depressive disorder with suicidal ideation (four patients). Coincidentally, all five cases exhibited treatment-resistant OCD, with a lack of an adequate response to high doses of different SRIs (administered for at least 3 months and potentiated by diverse antipsychotics) and to exposure and response prevention. Although mania or depressive symptoms improved in four patients, the OCD symptoms remained resistant to ECT in all patients, i.e., OCD's CGI Improvement Scale was ≥4. It is also worth noting that two patients described transient deterioration of their OCD symptoms following ECT, which led one of them to drop out of treatment before completion and the other to develop de novo obsessions with aggressive and sexual contents. Table 1 provides a description of these and other relevant OCD and ECT-related information pertaining to our sample.

DISCUSSION

Perhaps influenced by most current treatment protocols (which do not include ECT as a viable alternative in the management of OCD[3]), we recommended ECT to only 1.2% of our patients. Coincidentally, all five patients who were administered ECT had a history of minimal responses to several SRI trials potentiated with antipsychotics and to exposure and response prevention. Of note, in our case series, ECT was not prescribed to primarily manage underlying treatment-resistant OCD symptoms but rather to treat the associated acute mania and/or major depressive disorder with severe suicidal ideation. Accordingly, after ECT, four patients (80%) exhibited at least a partial remission of their mood disorder symptoms and two (40%) entered full remission. These findings are in broad agreement with previous studies showing a substantial response of both acute mania[10] and depression[11] to ECT. They also add further knowledge to the ECT literature by expanding the scenarios in which acute mania and depression are treatable by this potentially valuable therapeutic tool.

Although ECT was helpful in the treatment of mood disorders in the context of OCD, it typically did not lead to any therapeutic benefit for OCD symptoms per se. In fact, it was transiently detrimental in two (40%) of our patients. Specifically, although one patient reported short-lived de novo obsessions with aggressive and sexual contents, the other described more global deterioration of his OCD symptoms. It seems that OCD differs from major depression for failing to exhibit any significant response to more diffuse treatment techniques (e.g., ECT) but showing positive responses to stimulation of specific targets of the brain, such as in the case of deep brain stimulation of the ventral striatum, the subthalamic nucleus, or the inferior thalamic peduncle.[12] Indeed, although the efficacy of ECT in depression seems to stem from its effects on hypothalamus and hippocampus,[13] neurocircuitry targets in OCD are quite different, involving the orbitofrontal cortex and ventral striatum.

It is also intriguing that, despite sharing a positive response to SRIs, depression and OCD do not exhibit the same patterns of response to ECT. Although it has been shown that SRI should be administered in higher doses and for greater periods of time in OCD compared with depression,[14] it is not clear if further treatment modifications are required to increase the effectiveness of ECT in OCD. Indeed, it has been shown that response to conventional ECT in depression does not routinely involve changes in serotonergic activity,[15] an important component of several anti-OCD treatments. Potentially, other neurostimulation techniques (such as transcranial magnetic stimulation of specific brain regions and transcranial direct current stimulation) might, at least theoretically,

TABLE 1. Description of the Sociodemographic, Clinical, and Therapeutic Features of Patients With OCD Treated With ECT in Our Center

	OCD features				ECT data			
Patients (age and sex)	Age at OCD onset (years)	OCD predominant dimensions	Comorbidities	Previous adequate trials with SRI/antipsychotic augmentation	Primary indications for ECT	Total number of sessions/ frequency	Primary indication's response to ECT	OCD response to ECT
37-year-old man	29	Symmetry and ordering (e.g., need to touch, tap, or rub) Miscellaneous (e.g., self-mutilation)	Bipolar disorder	Fluoxetine 60 mg/day Paroxetine 60 mg/day Olanzapine 30 mg/day Thioridazine 500 mg/day	Acute mania	9 sessions/2 sessions per week	Full remission of acute mania symptoms	Transient worsening of OCD symptoms (CGI=6)
36-year-old woman	17	Aggressive and checking Miscellaneous (e.g., self-mutilation)	Body dysmorphic disorder Bipolar disorder Panic disorder Personality disorder not otherwise specified	Clomipramine 225 mg/day Paroxetine 60mg/d Sertraline 150 mg/day Fluvoxamine 150 mg/day Levomepromazine 700 mg/day	Depressive episode with suicidal ideation	9 sessions/2 sessions per week	Partial remission of depressive symptoms	No response (CGI=4)
55-year-old man	14	Contamination and washing Aggressive and checking	Major depressive disorder	Fluoxetine 80 mg/day Clomipramine 225 mg/day Risperidone 1 mg/day Mirtazapine 90 mg/day	Depressive episode with suicidal ideation	6 sessions 1–2 sessions per week	No response	Transient worsening of OCD symptoms (CGI=5)
56-year-old woman	20	Symmetry and ordering (e.g., repeating rituals) Aggressive and checking Contamination and washing	Bipolar disorder	Fluoxetine 60 mg/day Risperidone 2 mg/day Venlafaxine 450 mg/day	Depressive episode with suicidal ideation	19 sessions/2 sessions per week	Partial remission of depressive symptoms	No response (CGI=4)
35-year-old man	20	Miscellaneous (e.g., lucky/unlucky names, numbers, and dates)	Asperger syndrome Major depressive disorder	Sertraline 100 mg/day Imipramine 250 mg/day Fluoxetine 60 mg/day Risperidone 4 mg/day	Depressive episode with suicidal attempt	10 sessions/2 sessions per week	Full remission of depressive symptoms	No response (CGI=4)

CGI: Clinical Global Impression; OCD: obsessive-compulsive disorder; SRI: serotonin reuptake inhibitor.

promote greater changes in serotonergic systems[16] or in other OCD-relevant neural structures. Therefore, given the invasiveness and costs of treatments available for patients with treatment refractory OCD (i.e., DBS and neurosurgery), it is perhaps worth investigating other noninvasive brain stimulation approaches in OCD.

In the light of our present results, it seems clear that ECT, as currently administered, should be reserved for selected cases of patients with OCD displaying severe mood disorders. In addition, and despite these indications, clinicians should consider ECT's increased risk of worsening of OCD symptoms. In fact, when interpreting studies describing OCD patients with positive responses to ECT, one should consider that most of them were published a long time ago [even before effective treatments of OCD were available (e.g., SRIs)], included patients with atypical features (e.g., very late onset OCD),[7] and did not systematically incorporate standardized assessment methods of OCD [e.g., Yale-Brown Obsessive Compulsive Scale (YBOCS) and/or CGI].

Admittedly, our study has several limitations, including the small number of patients and other problems that are inherent to a chart review. Retrospective assessments are always dependent on the quality and completeness of the available information, which are rarely ideal. Because the indication for ECT in our patients was an intervening mood disorder, it could be argued that OCD symptom assessment was not a priority at the time of ECT administration. In fact, despite being assessed with a standardized tool (CGI), severity of OCD was not systematically evaluated with state-of-the art instruments, such the YBOCS.

Although our findings do not disprove the effectiveness of ECT in OCD, they call for further refinements in its indications. For instance, given that some OCD symptom dimensions appear to be more clearly related to depression (e.g., aggressive/checking and sexual/religious dimensions),[17] it remains to be established whether ECT or other neurostimulatory techniques are particularly effective for patients showing an specific pattern of OCD symptoms.

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3.3 TERCEIRO ARTIGO

“Prevalence and Correlates of Eletroconvulsive Therapy Delivered in 1001 Obsessive-Compulsive Disorder Outpatients”.

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Short communication

Prevalence and correlates of electroconvulsive therapy delivery in 1001 obsessive-compulsive disorder outpatients

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ABSTRACT

Individuals with obsessive-compulsive disorder (OCD) who sought treatment in seven different specialized centers (n=1001) were evaluated with a structured assessment battery. Thirteen OCD patients (1.3% of the sample) reported having been treated with electroconvulsive therapy (ECT) in the past. They were older and exhibited higher global severity of OCD symptoms, but were less likely to display symmetry/ordering and contamination/washing symptoms. They also had greater suicidality and increased rates of psychosis. Finally, OCD patients exposed to ECT were more frequently treated with antipsychotics, although they did not differ in terms of responses to adequate trials with serotonin reuptake inhibitors.

1. Introduction

There is an extensive list of neuropsychiatric conditions for which electroconvulsive therapy (ECT) is considered to be ineffective, including personality, somatoform, and obsessive-compulsive disorders (OCD) (Fink, 2008). Nevertheless, a recent review found that OCD patients continue to receive ECT for different reasons, including life threatening obsessive-compulsive symptoms, severe comorbidities, and treatment resistance, among other factors (Fontenelle et al., 2015). For instance, an OCD patient had received ECT for "walking compulsively on highways, often 50–60 km daily" (Nilsson and Ekselius, 2009). Similarly, major depression, increased suicidality, catatonia, mania, psychosis and agitation were often reported to be indications for ECT in OCD patients, as were previous positive responses to ECT and drug related side effects (Fontenelle et al., 2015). Yet, some of these scenarios (e.g. comorbid affective disorders and increased suicidality) are not uncommon in treatment seeking OCD samples (Torres et al., 2011) and may be equally reported in patients who have not been exposed to ECT during their lifetimes.

Given these superficial similarities between OCD patients who have and those who haven't been previously treated with ECT, it is important to clarify whether and how these two groups differ from each other. It is possible that features embedded within OCD phenotype (e.g. symptom dimensions) contribute to the patients' "odds" of being more "aggressively" treated. For instance, while OCD symptoms' dimensions associated with positive responses to conventional treatment may be less frequently reported in OCD patients treated with ECT, the presence of "violent and blasphemous" symptoms may be perceived as being more "risky" by patients and clinicians (Simonds and Thorpe, 2003). In this study, we aimed to: (i) describe the rates of past ECT use in a treatment seeking sample of 1001 OCD patients, and: (ii) investigate how patients treated with ECT differ from OCD patients who were not treated with ECT. By doing so, we expect to understand why clinicians continue to recommend and administer ECT for OCD patients despite the fact that ECT is not listed as a valid therapeutic alternative in many important treatment algorithms (e.g. Stein et al., 2012).

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2. Methods

Individuals with OCD who sought treatment in seven different specialized centers across five different Brazilian states were evaluated with an assessment package that included, among other information, relevant socio-demographic data, lifetime presence and severity ever of different OCD symptom dimensions (using the Dimensional Yale-Brown Obsessive-Compulsive Scale), severity of depression and anxiety, comorbidity rates using the Structured Clinical Interview for DSM-IV Psychiatric Disorders (SCID), and past treatment history (Miguel et al., 2008). Assessment of previous ECT treatments was standardized as "Have you ever been treated with ECT?".

All subjects signed an informed consent after an explanation of the procedures involved was given. The local institutional review boards approved this project, which was in full accordance with the declaration of Helsinki. Given the low numbers, we have performed Fisher's exact tests to compare frequencies of categorical variables and Mann-Whitney *U* test's to compare continuous variables between patients who were vs. who were not treated with ECT. The adopted level of significance was 0.05. No correction for multiple statistical comparisons was applied, considering the preliminary and exploratory nature of this investigation (Bender and Lange, 2001).

3. Results

Only 13 OCD patients (1.3% of the total sample) reported being treated with ECT during their lifetimes. They were compared to OCD patients who did not have a history of being treated with ECT in terms of socio-demographic features, symptom profiles, suicidality, comorbidity rates and treatment features (Table 1). Patients with OCD who were treated with ECT were generally older and had higher global severity levels during their worst illness period(s), but were less likely to exhibit symmetry/ordering and contamination/washing symptoms. They also had increased suicidality levels (including death whishes, suicidal thoughts and suicide plans) and greater rates of psychosis, which were particularly higher when both depression/mania associated psychosis and other psychotic disorders were collapsed as a single variable. In addition, OCD patients treated with ECT were more frequently treated with adequate trials of antipsychotics, although differences in terms of number of adequate serotonin-reuptake inhibitors (SRI) treatments failed to reach significance. In fact, rates of response to adequate SRI trials did not differ between the groups.

4. Discussion

Our findings indicate that only a small proportion of OCD outpatients (1.3%) had been treated with ECT. Importantly, these findings replicated the results of a previous study in which only 1.4% of OCD patients followed-up for up to 15 years received ECT[1] (Lins-Martins et al., 2015). Although we were unable to locate additional studies investigating the frequency of ECT use in other specialized OCD services, we believe these rates look reassuringly low compared to the ones that would be expected in affective and/or psychotic disorders outpatient clinics. The consistency of these numbers across independent samples is also noteworthy, considering that ECT utilization rates, practices and parameters vary greatly throughout continents, countries, or even regions within the same country (Leiknes et al., 2012), making ECT one of the most erratically used procedures in medicine (Hermann et al., 1995).

We have also found that OCD patients treated with ECT exhibited several distinguishing clinical features, including greater global OCD severity levels in the patients' most severe period, increased suicidality, and higher rates of psychosis, each already described as independent indications for ECT in OCD patients (Fontenelle et al., 2015). However, these features frequently overlap, and many OCD patients display combinations of more than one indication for ECT (Lins-Martins et al., 2015). The presence of a recognizable pattern of OCD features associated with the administration of ECT coupled with the stability of ECT treatment rates in two independent samples (the other being the one reported by Lins-Martins et al. (2015)) suggest that clinicians agree to a large extent on what constitutes an indication for ECT in OCD.

In terms of OCD symptoms, the contamination/washing and the symmetry/ordering dimensions were less frequently observed among OCD patients who received ECT. This finding is consistent with increased responses of these OCD dimensions to conventional treatments [such as exposure and response prevention, ERP (Abramowitz et al., 2003)]. However, they also suggest that clinicians may perceive contamination/washing and the symmetry/ordering symptoms as being less "risky" (perhaps as more stable or predictable) symptoms, thus not requiring a treatment as incisive as ECT. In support of this view is the fact that the rates of "objective" suicide attempts did not differ between OCD patients treated and not treated with ECT. This finding indicates that the prescription of ECT in OCD may be more closely linked to the "perception" of dangerousness, rather than to any objective evidence of it. Also, consistently with the latter hypothesis, we found a non-statistically significant hint towards a greater representation of sexual/religious symptoms as the "worst" symptoms reported by ECT-treated OCD patients, which we will discuss below.

Typically, OCD patients with sexual/religious symptoms have "phobia of impulses", i.e. fears of displaying unwanted and unacceptable behaviors as key ingredients to their symptoms. "Phobia of impulses" is also prevalent in patients with aggressive thoughts, which frequently load on the same factor as sexual/religious symptoms (Stewart et al., 2008), do not adhere to exposure and response prevention sessions (Santana et al., 2013) and are more often prescribed benzodiazepines (Starcevic et al., 2016). Sexual/religious symptoms have also been found to be marginally more frequent in OCD patients who were resistant to ERP (Rufer et al., 2006) as well as significantly more frequent in OCD patients who were refractory to both ERP and pharmacotherapy (Ferrao et al., 2006).

OCD patients treated with ECT were typically more often prescribed an adequate trial of antipsychotics, although only marginally more likely to be managed with adequate trials of SRIs. Perhaps the fact that ECT patients were more psychotic and suicidal, in association with a clinician's fear of aggravating psychosis with SRIs, may be at the root of this finding, thus hindering OCD patients from being more frequently exposed to adequate trials with SRIs. Nevertheless, the fact that rates of response to pharmacotherapy did not differ between ECT vs. non-ECT OCD patients suggest that, in our sample, features other than treatment resistance may explain why patients with OCD had been treated with ECT. Since these OCD patients reported ECT treatments that were often performed before they were seen in our OCD clinics, these results could well reflect some degree with unfamiliarity with recognized anti-OCD treatments by clinicians who have treated these patients in the past.

Our study has a number of drawbacks. For instance, most reports of previous treatment histories did not entail a cross-referencing with actual patient records to confirm they have actually happened. Also, we were unable to establish previous responses to ERP, since the variable "history of psychotherapy" could be anything from ineffective talk therapy to evidence-based ERP. Most importantly, however, was the difficulty in establishing clear links between specific socio-demographic and clinical features to past use of ECT, which may not have coincided in a particular time

[1] Although 37 patients from the present study were included in the Martins-Lins study, only 1 of them had a history of ECT use, and none of them were prospectively treated with ECT in the later study.

Table 1
Comparisons of socio-demographic features, symptom profiles, suicidality, comorbidity rates and treatment features between OCD patients who weren't and were treated with ECT at some point during their illness.

Variables of interest	OCD patients not treated with ECT (n=988)		OCD patients treated with ECT (n=13)		Statistics
Sociodemographic features	N	%	N	%	
Age (mean yrs ± SD)*	34.7 ± 12.9*		43.4 ± 16.2		Z= −1.9; p=0.05
Gender					Fisher's p=0.78
Male	427	43.2	5	38.5	
Female	561	56.8	8	61.5	
Marital status					Fisher's p=0.29
Married, *de facto*, or widowed	388	39.3	3	23.1	
Single or divorced	600	60.7	10	76.9	
Occupation					Fisher's p=0.09
Unemployed	491	49.8	10	76.9	
Employed	494	50.2	3	23.1	
Education (mean yrs ± SD)	14.5 ± 4.9		13.9 ± 6.2		Z= −0.4; p=0.72
Comorbid symptom severity					
Beck Depression Inventory	16.5 ± 11.6		16.7 ± 8.4		Z= −0.3; p=0.72
Beck Anxiety Inventory	16.0 ± 11.7		13.7 ± 5.9		Z= −0.3; p=0.78
OCD Symptoms					
Age at onset (mean yrs ± SD)	12.5 ± 7.23		12.6 ± 6.5		Z= −0.3; p=0.78
Lifetime rates of OCD symptoms					
Aggression	609	62.4	8	61.5	Fisher's p=0.58
Sexual/Religious	527	53.9	9	69.2	Fisher's p=0.21
Symmetry/Ordering*	830	85.0	8	61.5	Fisher's p=0.03
Contamination/Washing*	700	71.6	5	38.5	Fisher's p=0.01
Hoarding	479	49.0	5	38.5	Fisher's p=0.32
Miscellaneous	829	84.9	11	84.6	Fisher's p=0.60
Current worst OCD symptom					
Aggression	155	15.9	2	15.4	Fisher's p=0.66
Sexual/Religious	117	12.0	4	30.8	Fisher's p=0.06
Symmetry/Ordering	196	20.1	2	15.4	Fisher's p=0.50
Contamination/Washing	207	21.2	2	15.4	Fisher's p=0.46
Hoarding	51	5.2	1	7.7	Fisher's p=0.51
Miscellaneous	256	26.3	2	15.4	Fisher's p=0.30
Severity of OCD symptoms in worst phase					
Aggression (mean ± SD)	6.73 ± 5.55		6.62 ± 6.05		Z= −0.9; p=0.93
Sexual/Religious (mean ± SD)	5.65 ± 5.64		7.85 ± 6.08		Z= −1.3; p=0.16
Symmetry/Ordering (mean ± SD)	8.77 ± 4.74		8.46 ± 5.44		Z= −0.2; p=0.84
Contamination/Washing (mean ± SD)	7.64 ± 5.47		6.69 ± 6.73		Z= −0.3; p=0.72
Hoarding (mean ± SD)	3.90 ± 4.59		3.00 ± 5.00		Z= −0.8; p=0.93
Miscellaneous (mean ± SD)	8.88 ± 4.82		7.92 ± 5.69		Z= −0.5; p=0.60
Total global (mean ± SD)*	23.6 ± 5.06		25.9 ± 5.28		Z= −2.1; p=0.03
Suicidality					
Had already thought life was not worth living	559	59.0	10	83.3	Fisher's p=0.13
Had already wished to be dead*	429	45.3	9	75.0	Fisher's p=0.04
Had already presented suicidal thoughts*	340	35.9	8	66.7	Fisher's p=0.03
Had already made suicidal plans*	193	20.4	6	50.0	Fisher's p=0.02
Had already attempted suicide	101	10.7	3	25.0	Fisher's p=0.13
Had current suicidal thoughts	101	10.7	3	25.0	Fisher's p=0.13
Past history of comorbidity					
Bipolar I disorder	33	3.3	0		Fisher's p=1.00
Bipolar II disorder	38	3.9	1	7.7	Fisher's p=0.40
Major depressive episode	555	56.2	10	76.9	Fisher's p=0.16
Associated psychotic symptoms*	21	2.1	2	15.4	Fisher's p=0.03
Plus psychotic disorders*	7	0.7	2	15.4	Fisher's p=0.005
Dysthymic disorder	115	11.6	3	23.1	Fisher's p=0.19
Alcohol use disorder	78	7.9	1	7.7	Fisher's p=1.00
Panic with agoraphobia	95	9.6	1	7.7	Fisher's p=1.00
Panic without agoraphobia	59	6.0	1	7.7	Fisher's p=0.55
Agoraphobia without panic	49	5.0	0		Fisher's p=1.00
Social anxiety disorder	340	34.4	5	38.5	Fisher's p=0.77
Specific phobia	309	31.3	5	38.5	Fisher's p=0.56
Posttraumatic stress disorder	188	19.0	2	15.4	Fisher's p=1.00
Generalized anxiety disorder	339	34.3	4	30.8	Fisher's p=1.00

Table 1 (*continued*)

Variables of interest	OCD patients not treated with ECT (n=988)		OCD patients treated with ECT (n=13)		Statistics
Treatment features & outcomes					
History of psychotherapy	632	64.0	11	84.6	Fisher's p=0.15
History of at least 1 positive SRI trial	233	23.6	4	30.8	Fisher's p=0.52
Mean number of total adequate SRI trials (mean ± SD)	0.71 ± 1.00		1.61 ± 1.70		Z=−1.9; p=0.06
Mean number of total adequate AP trials (mean ± SD)*	0.10 ± 0.43		0.92 ± 1.93		Z=−4.1; p<0.001
Resistance to at least 2 adequate SRIs trials	131	77.5	3	60.0	Fisher's p=0.32
Resistance to least 1 adequate AP trial	61	80.3	4	80.0	Fisher's p=1.00
Resistance to at least 2 adequate SRIs plus 1 adequate AP trial	22	57.9	1	50.0	Fisher's p=1.00

SRI: Serotonin Reuptake Inhibitor; AP: Antipsychotic. *p <=0.05

point. For instance, we cannot guarantee that OCD patients who received ECT have develop some of their distinguishing features (e.g. psychosis or worse global severity) after, rather than before, ECT utilization. Thus, to interpret these findings as correlates (or "indications") for ECT administration in OCD might be considered speculative. However, in an attempt to overcome this limitation, we have used "lifetime" comorbidities and "worst ever" DYBOCS symptom severities as target variables, assuming that ECT was likely to have been prescribed during periods of greater comorbidity rates and/or clinical gravity.

The low numbers of ECT utilization in our OCD clinics might simply represent a referral bias, i.e. OCD patients who were more severely depressed, suicidal or psychotic might have been more likely to be referred to alternative clinics focusing in affective or psychotic disorders or even admitted to inpatient units. However, psychosis was not an exclusionary criterion in our protocol, as long as patients were not acutely ill. Also, all sites were tertiary services, which usually receive moderate to severe cases. Finally, the high number of associations tested in this exploratory study increases the likelihood of type 1 error, but, on the other hand, the small number of patients with past history of ECT may have affected the study power (type 2 error). For example, lifetime major depression was more frequent among OCD patients that had received ECT than among the other patients (77% vs. 56%), but this difference did not reach statistical significance.

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3.4 QUARTO ARTIGO

“An Interim Analysis of a Double-Blind Sham-Controlled Study on the Acute Effects of Transcranial Direct Current Stimulation in Obsessive-Compulsive Disorder”.

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An interim analysis of a double-blind sham-controlled study on the acute effects of transcranial direct current stimulation in obsessive-compulsive disorder

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ABSTRACT

BACKGROUND: We describe the interim analysis of a double-blind sham controlled quasi-randomized study on the acute effects of transcranial direct current stimulation (tDCS) for individuals with obsessive-compulsive disorder (OCD).

METHODS: Twenty OCD patients were assigned to receive a single session of sham (n=10) or active (2mA) tDCS (n=10) for 30 minutes, with the cathode placed over the central supplementary motor area (SMA) and the anode on the supraorbital region. Assessments of outcome were made at baseline and one hour following tDCS using: a dot-probe task comprising images illustrating different OCD-related scenarios, the Positive and Negative Affect Schedule (PANAS), and the Yale-Brown Obsessive-Compulsive Challenge Scale (YBOCCS; a measure of symptoms in the preceding hour).

RESULTS: Active and sham tDCS groups did not differ in terms of age, gender, medication use and baseline severity of OCD, depression and anxiety symptoms. Though a significant time-effect (before vs. after tDCS) was observed on YBOCCS, PANAS and dot-probe scores, there was no interaction between groups. However, exploratory analyses revealed that sham tDCS led to a significant decrease in OCD symptoms in the past hour, while active tDCS did not.

CONCLUSIONS: Although we did not observe acute effects of tDCS on OCD symptoms, this interim analysis suggests that inhibition of the SMA may interfere with sham response in OCD, probably through increasing vigilance towards OCD-related environmental stimuli.

INTRODUCTION

Obsessive-compulsive disorder (OCD) is a relatively common and chronic condition characterized by unwanted and persistent thoughts, images, or urges (obsessions) and/or repetitive motor behaviours or mental acts that are performed to reduce anxiety/distress or according to certain rules (compulsions) [1]. Although a significant proportion of OCD patients respond to traditionally available treatments (such as serotonin reuptake inhibitors and/or exposure and response prevention), up to 30% remain significantly symptomatic despite adequate treatment [2,3]. Recently, a range of neurostimulatory techniques, such as repetitive transcranial magnetic stimulation (rTMS) and deep brain stimulation (DBS) have been proposed as new treatments for OCD [4,5]. However, the exact sites and ideal parameters to be employed by these different techniques remain elusive.

A number of studies have suggested a role for the supplementary motor area (SMA) in the pathophysiology of OCD. In one early fMRI study, OCD patients had greater activations of the SMA and deactivations of the rostral anterior cingulate during high- vs. low-conflict trials [6]. Similarly, increased activity in the left pre-SMA during successful stop-signal inhibition was reported both in OCD patients and in their unaffected siblings as compared to healthy subjects, suggesting that abnormal activity within the SMA may be in fact an endophenotype for OCD [7]. Although hyperactivity within the SMA was initially considered compensatory [as it correlated negatively both with neuronal N-acetylaspartate levels in the dorsal anterior cingulate region [6] and with stop-signal reaction times [7]], most trials targeting the SMA with low-frequency (1 Hz) rTMS stimulation (inhibitory) in OCD have proved effective [8,9].

Interest on the utility of transcranial direct current stimulation (tDCS) across different psychiatric disorders has grown exponentially in the last few years owing to its favourable tolerability, portability and affordability profile [10]. tDCS delivers low-amplitude direct currents that penetrate the skull from the anode, travel throughout the brain tissue, and exit the skull via the cathode, although its neurobiological mechanisms of action are still not entirely clear [11]. Based on the potential role of SMA and the utility of low-frequency TMS in OCD, we thought would be intuitive to test the efficacy of a tDCS cathode (inhibitory) placed over the SMA of OCD patients (as suggested by [12,13]).

If SMA hyperactivity in OCD patients is a primary phenomenon, novel treatments that result in inhibition of the SMA could be therapeutically efficacious. However, if the SMA hyperactivity exhibited by OCD patients is purely compensatory (i.e. aimed at minimizing OCD symptoms), a tDCS session aimed at inhibiting the SMA activity should lead to worse

obsessive-compulsive symptoms. Given the current uncertainties about the effects of tDCS in OCD patients, we thought it would be advisable and safer to firstly test the acute results of a single tDCS session over the patients' symptoms. We acknowledge, though, that the existence of an effect of a single tDCS session over other emotional states has been disputed, at least in healthy populations [14]. To clarify these important questions, we describe the interim analysis of a double-blind sham controlled quasi-randomized study on the acute effects of a single tDCS session in OCD patients.

METHODS

Patients

Twenty OCD patients who remained symptomatic despite stable pharmacological treatment regimens for at least three months were consecutively recruited from individuals being treated at the Anxiety, Obsessive, and Compulsive Research Program of the Institute of Psychiatry of the Federal University of Rio de Janeiro (IPUB/UFRJ). All volunteers signed an informed consent form agreeing to participate in the project, which was approved by the local ethics committee and registered in the Brazilian Registry of Clinical Trials (*RegistroBrasileiro de EnsaiosClínicos*) under the # RBR-6y4ghx

Subjects were selected according to the following inclusion criteria: (1) a diagnosis of OCD confirmed by the Structured Clinical Interview for Axis I DSM-IV Disorders (If a comorbid diagnosis was present, OCD had to be associated with greatest severity of symptoms and earlier age at onset); (2) age between 18 and 60 year old; (3) at least basic (primary) education; and (4) a Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) > 16 (at least moderate severity) despite treatment with at least one serotonin reuptake inhibitors administered in maximum tolerated dose for at least 12 months.

The exclusion criteria comprised: (1) having epilepsy or seizure disorders; (2) having brain tumours, cysts, or any other medical comorbidity thought to interfere with the purposes of our study; (3) having severe personality disorders, and (4) having intellectual disability according to the assisting clinician. Patients who were using benzodiazepines were not excluded but asked to withhold their dose on the day before their participation of the project. Though only 20 patients were included to date, we expect to include 50 patients. A detailed description on the steps involved in the research protocol is provided in table 1.

INSERT TABLE 1 ABOUT HERE

Behavioural assessment

Measurement of baseline severity of symptoms

Patients had the severity of obsessive-compulsive, anxiety, and depression symptoms assessed by means of the self-report version of the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) [15,16], the Beck Anxiety Inventory (BAI) [17], and the Beck Depression Inventory (BDI) [17].

Measurement of Acute Changes in Obsessive-Compulsive Symptoms

As one of the critical features of OCD is the time spent with symptoms, any scale used to measure acute changes in OCD symptom severity need to be adapted to take that into account. It has been suggested that a 60-minute interval represents the shortest time period over which OCD symptom severity can be assessed without seriously compromising reliability. [18] In our study, we used the Yale Brown Obsessive-Compulsive Challenge Scale (YBOCCS), [18] a self-report visual analogue scale containing 10 items covering severity of OCD symptoms in the past hour, as a *primary* outcome measure.

In the Y-BOCCS, each item is visually rated according to anchors provided to indicate severity varying from 0 (none) to 4 (extreme). Total scores vary from 0 to 40. Items include time spent on obsessions, anxiety due to obsessions, time spent on compulsive behaviours, intensity of the compulsion to perform the behaviour, degree of indecisiveness (difficulty in choosing between simple alternatives), guilt (concerned that did or will do something terrible or wrong), degree of control over obsessivethoughts and/or compulsive behaviours, conviction that something awful with happen unless behaviour is performed, and overall severity of obsessions and compulsions.

Measurement of Acute Changes in Affective States

Patients had their current and lifetime affective states measured by the Positive and Negative Affective Schedule (PANAS) [19], a 20-item scale including 10 positive and 10 negative feelings and emotions, each rated on a five-point likert scale ranging from 1 (very slightly or not at all) to 5 (extremely).

Attentional bias task

Attentional bias, i.e. the tendency to focus attention on specific stimuli, may refer to the quickness of spotting ("attentional facilitation" or "increased vigilance") or to the slowness of distracting ("difficulty in disengaging") from specific (e.g. threatening) as compared to other (e.g. non-threatening) types of stimuli [20]. There is evidence suggesting that both types of attentional biases may be involved in the pathophysiological mechanisms leading to and/or maintaining OCD [2122]. For instance, in one study, individuals with high contamination fears displayed attentional facilitation to contamination-related stimuli [23]. In the present study, we have employed an attentional bias (dot-probe) task that involved multiple OCD-related threating pictures (as detailed in Sizino da Victoria et al. submitted).

Briefly, patients seated in front of a computer screen showing six blocks of 60 pairs of stimuli consisting of one threatening (OCD-related) picture (illustrating different washing, checking, obsessing, ordering, neutralizing, and hoarding scenarios) and one neutral but equally complex picture or two neutral equally complex pictures. There was no break between the blocks. Each picture appeared side-by-side for 500 ms.Once these stimuli disappeared, a dot appeared either at the location of the former OCD related stimulus in 120 congruent trials, at the stimulus in 120 incongruent trials or at the location of one of two neutral stimulus in 120 neutral trials, i.e. trials showing two paired neutral pictures. Participants' reaction times to indicate the side where dot appeared were recorded. Reaction times values in congruent and incongruent trials were corrected (divided) by reaction times in neutral trials and, together with Y-BOCCS scores, used as primary outcome measures. Shorter reaction times in congruent trials indicated "attentional facilitation" or "increased vigilance" for OCD-related stimuli, and longer reaction times in incongruent trials indicated "difficulty disengagement" from OCD-related stimuli [22].

tDCS procedure

The tDCS session was performed with DC stimulator plus device from Neuroconn®. The neurostimulator comprised one rechargeable battery and two rubber electrodes with opposed poles (cathode - /anode +) connected with two cables. The cathode (8 cm^2) was placed 2 cm anteriorly from Cz and the anode (40 cm^2) was placed over the central supraorbital ridge (corresponding to SMA and OFC, respectively, according to the International 10-20 electroencephalography system). A large anode was chosen to render stimulation over the OFC functionally inefficient, [24] given its well-established role in the pathophysiology of OCD.

[25,26]To guarantee adequate conductibility and safety, the electrodes were soaked in a salinized (0.9%) solution, involved in a protecting sponge, and fixed with a headband.

Patients were instructed to remain seated in a confortable position until the end of the procedure. The active tDCS group received a current of 2 mA for 30 min, while the sham tDCS receive a current of 2 mA for 30 seconds, which was then was turned off. This strategy aimed to mimic in the sham tDCS common adverse effects of itching that are experienced immediately after stimulation onset, thus increasing blindness. To maximize tolerability, current increases in the beginning and decreases at the end of the sessions were done along 10 seconds. A psychiatrist (NLM) administered the tDCS session and supervised the ratings. A researcher with biomedical degree (SSR) was responsible to assign patients to active or sham groups in alternate fashion, turning on and off the device without the tDCS administers knowledge. Participants' blindness was assessed with a specific scale, described below [27].

Measurement of tDCS adverse effects

At the end of the tDCS session, patients answered the YBOCCS, the PANAS, and the tDCS Adverse Effects Questionnaire. [27] The latter instrument includes a list of adverse effects that were commonly reported in a range of tDCS studies, such as headache, neck pain, scalp pain, tingling, itching, etc. Patients respond whether they have experienced any of the adverse effects listed, their intensity (from 1-absent to 4-severe) and whether they believe they were related to tDCS (from 1-not at all to 5, definitely). In our study, we have reported whether patients experience any side effect and the intensity of the worse side effect.

Statistical Analysis

Baseline features were compared between patients assigned to active or sham tDCS with chi-square or Fisher's exact test (when variables were categorical) or Mann-Whitney U tests (when variables were continuous). Repeated measures ANOVA was used to compare groups (active and sham tDCS) and YBOCCS scores, PANAS positive and negative affects scores and dot-probe reaction time indexes before and after the intervention. The adopted level of significance was .05.

RESULTS

Active and sham tDCS groups did not differ in terms of age, gender, medication use, and baseline severity of OCD, depression and anxiety symptoms (table 2). Although patients who were treated with active tDCS correctly guessed which group they were assigned to more often than patients treated with sham tDCS (90% vs. 50%), this difference failed to reach

statistical significance (Fisher's exact test p=0.14; two tailed). In addition, groups did not differ in relation to intervention-related tolerability, neither in terms of presence of any adverse effect (tDCS group n=10, 100%; sham tDCS group n=9; 90%; Fisher's exact test p=1.0; two tailed) nor in the greatest intensity of the experienced adverse effect (Z=-0.53; p 0.59; two tailed).

INSERT TABLE 2 ABOUT HERE

A significant time-effect (before vs. after intervention) was observed in relation to YBOCCS scores [*F* (1, 18) = 15.72, p = .001], vigilance [*F* (1, 18) = 4.21, p = .05], disengagement [*F* (1, 18) = 5.94, p = .02], and PANAS negative [F (1, 18) = 9.53, p = .006] scores, with decreases in all outcome measures. However, no time-effect was noted in relation to PANAS positive scores [*F* (1, 18) = 0.83, p = .37]. Further, we were unable to note an interaction between group (active vs. sham tDCS) and time (before vs. after intervention) in terms of YBOCSS (*F* (1, 18) = 1.91, p = .18), vigilance [*F* (1, 18) = 1.90, p = .18], disengagement [*F* (1, 18) = 1.37, p = .25] and PANAS negative scores [*F* (1, 18) = 0.15, p = 0.70] (see figures 1-5).

Supplementary exploratory analyses revealed that sham tDCS led to a significant decrease in OCD symptoms in the past hour (Z=-2.48; p= .01), while active tDCS did not (Z=-1.68; p= .09). Significant decreases in PANAS negative affect were also seen in sham and active tDCS (Z=-2.13; p= .03 and Z=-2.20; p= .03, respectively). While active tDCS resulted in a significant decrease in the ratio between reaction times in congruent trials /neutral trials, indicating increased vigilance (Z=-2.20; p= .03), no significant change in vigilance was seen in the group submitted to sham tDCS (Z=-0.56; p= .57). Finally, both sham and active tDCS failed to result in significant changes in terms of disengagement (Z=-1.07; p= .28 and Z=-1.6; p=0.09).

DISCUSSION

This report describes the interim analysis of a double-blind sham controlled between groups study on the acute effects of cathodal SMA tDCS in OCD patients. Although our main analysis failed to demonstrate significant differences between active and sham tDCS treatments in the primary outcome measures, supplementary analyses seem to suggest that active tDCS may have interfered with sham/placebo response in OCD and that this effect was possibly due increasing vigilance towards OCD-related environmental stimuli. Our supplementary analyses

also suggested that this interference was independent from decreases in PANAS negative affect and from the ability to disengage from OCD relevant stimuli. Apparently, interference with the expected sham/placebo response in our study was also unrelated to adverse effects experienced by the active tDCS group, which did not seem to differ in terms of frequency and intensity from the sham tDCS patients.

Although preliminary, one interpretation of our findings is that the inhibition of SMA may interfere negatively with response to sham tDCS in OCD. They are consistent with a few case reports and series showing that other tDCS montages with the anode placed in the pre-SMA [28,29] or the cathode placed in the OFC [30,31] may be therapeutically effective in treatment resistant OCD patients. Our findings also suggest that hyperactivity of the SMA may be a compensatory phenomenon resulting from primary pathophysiological events occurring elsewhere in the brain, as initially suggested by at least two previous fMRI studies [6,7]. However, we cannot exclude the possibility that, by placing the anode on the supraorbital area, we have stimulated the OFC, an area known to be hyperactive in OCD. Although we have attempted to minimize the stimulatory effects over OFC with a large electrode, one study reported that anodal tDCS of the OFC resulted in less interference in an emotional Stroop task in healthy volunteers (which was also independent from any effect on mood), [32] thus supporting the idea that increased activity of the OFC in OCD can lead to increased vigilance. Accordingly, by being excessively attentive to the perceived sources of threat, OCD patients may be more prone to develop and/or maintain their symptoms [21].

Our report has a number of limitations. Firstly, it includes an interim analysis of only a few OCD patients (n=20) who were recruited as a part of a larger study, targeting more than twice the present number of subjects (n=50). Thus, although our findings suggest a hint toward significance, we acknowledge that our OCD patients' profile can change with further recruitment, i.e. results may not necessarily become significant with the expansion of the sample. However, we believe this is unlikely, as all patients are generally selected from the same OCD clinic. Secondly, patients' blinding was not optimal, i.e. patients who were allocated to the active tDCS group correctly guessed their intervention more often than patients who were allocated to sham tDCS. Therefore, one could argue that the lower decreases in OCD symptoms seen in the former group may reflect some sort of "nocebo" response induced by an expectation of detriment or harm in patients assigned to tDCS. [33]

In relation to the later interpretation, we cannot exclude the possibility that improvements (particularly decreases in PANAS negative scores) were also related to the end of a procedure perceived as potentially threatening by anxious OCD patients. In spite of these

potential drawbacks, it should be kept in mind that this report describes the interim results of the first double-blind sham-controlled study on the acute efficacy and tolerability of tDCS in OCD. Once concluded, this study will help to establish the best protocols to be used in future and longer double blind controlled investigations of tDCS in OCD, such as the optimal current, the stimulus duration, and the size and positions of the electrodes to be employed in such patients. If the hints observed in this analysis hold true, it would be probably be wise to test in the future a montage with the tDCS anode placed over the SMA and the cathode placed in an extracephallic region or in an area that has not demonstrated any major involvement in the pathophysiology of OCD (e.g. the occipital region).

Table 1: Description of the procedures involved in the study

	Baseline assessment and tDCS set-up	**Dot-probetask**	**Active orshamtDCS**	**Dot-probetask**	**Post Dot-probetask**	**Resting time**	**End-point assessment**
Duration (minutes)	30	20	30	20	5	35	5
Questionnaires andscales	YBOCS BDI BAI YBOCCS PANAS		Sideeffectsassessment		PANAS		YBOCCS

Footnote: tDCS=transcranial direct current stimulation; YBOCS=Yale-Brown Obsessive-Compulsive Scale; BDI=Beck Depression Inventory; BAI=Beck Anxiety Inventory; YBOCCS=Yale Brown Obsessive-Compulsive Challenge Scale; PANAS=Positive and Negative Affective Scale.

Table 2: Comparison between baseline and endpoint features of OCD patients treated with active vs. sham tDCS

	Active tDCS (n=10)		**ShamtDCS (n=10)**		**Statistics**
Gender (n; % male)	5 (50%)		5 (50%)		X2=0.0; df=1; p=1.0
Use of SRI	10 (100%)		10 (100%)		___
Use ofantipsychotics	6 (60%)		6 (60%)		Fisher'sexacttest p= 1.00
Use ofbenzodiazepines	7 (70%)		4 (40%)		Fisher'sexacttest p= 0.37
	Mean	**S.D**	**Mean**	**S.D.**	
Age	42.1	12.8	37.8	10.6	Z= -0.64; p=0.51
Age ofonset	16.8	11.4	11.3	5.5	Z= -1.18; p=0.24
YBOCS	25.9	3.2	25.1	3.3	Z= -0.72; p=0.47
BAI	18.4	9.4	13.8	8.3	Z=-1.10; p=0.27
BDI	21.8	9.6	18.0	10.4	Z=-0.95; p=0.34
PANAS					
Negative affectlifetime	20.0	10.5	21.3	10.4	Z=-0.19; p=0.85
Positive affectlifetime	19.5	5.6	17.3	8.2	Z=-0.83; p=0.40
SRI score*	36.6	17.0	31.5	10.4	Z=-0.59; p=0.55
Antipsychotic score*	9.6	11.4	7.1	9.8	Z=-0.34; p=0.73
BASELINE scores					
YBOCCS	33.7	16.1	31.1	14.1	Z= -0.53; p=0.60
PANAS negative	13.0	11.1	10.5	9.2	Z=-0.45; p=0.65
PANAS positive	16.7	8.1	12.8	8.0	Z=-1.00; p=0.32
ENDPOINT scores					
YBOCCS	27.0	10.8	17.3	15.6	Z=-1.66; p=0.10
PANAS negative	8.1	6.1	6.7	5.5	Z=-0.80; p=0.42
PANAS positive	16.6	8.5	14.9	9.3	Z=-0.53; p=0.59

Footnote: SRI score: serotonin reuptake inhibitor relative dose; antipsychotic score: antipsychotic relative dose.

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4. CONSIDERAÇÕES FINAIS

Após a revisão dos principais métodos neuroestimulatórios disponíveis no TOC e apresentação do material científico produzido, torna-se relevante destacar alguns aspectos. Até o presente momento, o único método neuromodulatório aprovado pelo *Food and Drug Administration* para uso em pacientes com TOC é a estimulação cerebral profunda (YOUNGERMAN et al., 2016). Dado o seu caráter invasivo, é o método que mais aproxima-se das cirurgias ablativas, que também são uma alternativa aos casos refratários, porém com a vantagem da sua reversibilidade (GREENBERG; RAUCH; HABER, 2010). O uso de diferentes alvos estimulatórios prioriza realizar um efeito inibitório em regiões estriado-talâmicas, tendo sido alcançados resultados satisfatórios.

Muitos estudos foram conduzidos em região da CV/EV, mais posterior, dado ao fato de esta região anatômica estar intrinsecamente relacionada aos neurocircuitos do TOC (GREENBERG BD et al., 2010). A região subtalâmica mostrou-se bastante eficaz, no entanto, foi durante a estimulação deste último alvo que ocorreram efeitos adversos mais graves (MALLET et al., 2008). Apesar de ser o único método estimulatório aprovado até o momento para tratamento do TOC, ainda não possui padrões definidos, inclusive no que se refere ao melhor alvo a ser estimulado (MORISHITA et al.,2014). O mecanismo de ação exato por meio do qual a ECP atua continua desconhecido.

Outra técnica de neuromodulação abordada nesta dissertação foi a eletroconvulsoterapia. Apesar do uso da ECT ter a sua finalidade bem definida na prática clínica da maioria dos transtornos psiquiátricos, o mesmo não ocorre em relação ao TOC. A literatura da ECT no TOC é composta, em sua maioria, de relatos de casos e séries de casos que apresentam resultados favoráveis à prática. Todavia, a partir da realização do estudo de revisão sistemática do nosso grupo (FONTENELLE et al., 2015), que já foi apresentado, percebemos que tanto os artigos mais antigos quanto os mais recentes, não utilizaram metodologia adequada para avaliação de resposta, dentre outras falhas. Fazendo uma análise individual nestes estudos, apenas 2,5% dos casos tiveram o YBOCS reportado, sendo esse o principal instrumento para identificar resposta terapêutica no TOC. Outro dado relevante, é que mesmo os estudos mais recentes não mostraram realização de tratamento adequado com IRSs, e apenas 16,9% relataram dose e duração do tratamento farmacoterápico (FONTENELLE et al., 2015).

A partir da constatação de um tratamento convencional inadequado nestas pesquisas com a ECT, não podemos considerar que os pacientes com TOC que foram submetidos a esta técnica neuroestimulatória sejam refratários. Como parte destes indivíduos realizaram a ECT

antes do conhecimento e uso disseminado dos IRSs, pode-se supor que, atualmente, a maioria não teria indicação de realizar esta técnica neuromodulatória. Na série de casos também apresentada neste trabalho, identificou-se que 1,2% dos pacientes de uma mesma clínica foram elegíveis para a realização do procedimento (LINS-MARTINS et al., 2014). Este baixo percentual corrobora com o encontrado no estudo de Dos Santos-Ribeiro e colaboradores (2016), que abrangeu sete clínicas especializadas em cinco estados brasileiros e também encontrou uma baixa taxa de indicação de ECT em pacientes com TOC.

Portanto, não podemos constatar a eficácia da ECT no TOC. Não há estudos controlados-randomizados nesta área e diante das novas técnicas como a ECP que mostram resultados consistentes e promissores, não parece haver finalidade em dar prosseguimento a este campo da pesquisa. Desde a década de 80, estudos de revisão já consideravam a ECT como sendo um método contraindicado para o tratamento do TOC (FINK, 1982). Todavia, devemos considerar que pacientes com este transtorno e comórbidos com o TAB podem ser um desafio na prática clínica. Como também foi descrito nos estudos de Lins-Martins e colaboradores (2014) e Dos Santos-Ribeiro e colaboradores (2016), a maioria das pessoas com TOC foram submetidas à ECT por concomitante transtorno do humor. Desse modo, pacientes com sintomas obsessivos-compulsivos graves e diagnóstico de TAB, são suscetíveis a beneficiar-se do tratamento com ECT em episódios de mania ou depressão.

Em relação à EMTR, os primeiros estudos utilizaram como alvo a região do córtex pré-frontal dorsolateral (GREENBERG et al., 1997; ALONSO et al., 2001). Como já foi visto nesta dissertação, a escolha do alvo baseou-se em estudos bem-sucedidos de EMTR na depressão maior, visto que o córtex pré-frontal também faz parte da fisiopatologia do TOC (BAIS; FIGEE; DENYS, 2014; ARONSON et al., 2014). O uso da EMTR de baixa frequência foi preferencialmente adotado, considerando-se a hiperexcitabilidade cortical no TOC, apesar do funcionamento deste neurocircuito ainda ser pouco conhecido. (BERLIM; NEUFELD; VAN DEN EYNDE, 2013). No entanto, em 2010 uma metanálise propôs que não seja mantida a indicação de uso da EMTR para o TOC em região do CPFDL, dado os resultados conflitantes dos nove estudos controlados-randomizados analisados (SLOTEMA et al., 2010). Ainda levando-se em consideração pesquisas de neuroimagem funcional, que também mostraram hiperatividade em córtex orbito frontal medial no TOC, os alvos promissores tornaram-se o COF e, mais especificamente, a AMS (YÜCEL et al., 2007).

Por ser uma região anatomicamente mais acessível do que o COF, a área pre-motora/motora suplementar tornou-se alvo da maioria dos estudos mais recentes de EMTR no TOC, com resultados positivos na redução dos sintomas quando usada a EMTR de baixa

frequência (MANTOVANI et al., 2006, 2010). Estudos de metanálise constataram que o método pode ser usado como uma terapia adjuvante ao uso dos IRS. Portanto, não pode ser considerado superior às estratégias de associação de IRS aos antipsicóticos ou às terapias de exposição e prevenção de resposta (BERLIM; NEUFELD; VAN DEN EYNDE, 2013). Apesar de uma tendência a considerar a EMTR de baixa frequência na AMS, os estudos controlados-randomizados, até o momento, não comprovam esta eficácia, pois são ensaios clínicos com parâmetros heterogêneos e amostras pouca satisfatórias. Um *guideline* da comissão europeia de 2014 traz a EMTR com nível de evidência classe A ("comprovadamente eficaz") em depressão maior, porém relata que ainda não é possível fazer nenhuma recomendação de protocolo no TOC (ROSSI et al., 2009).

Seguindo a expectativa de desenvolver métodos não-invasivos como terapia adjuvante ou como monoterapia no TOC, devemos destacar a importância dos estudos que vem sendo propostos com a ETCC. Além de comparações conceituais que podem ser feitas com a EMTR, muito do seu embasamento na prática clínica vem sendo determinado a partir do que se pode extrair de estudos com EMTR no TOC. Apesar de ainda possuir uma literatura muito escassa e recente, com artigos heterogêneos, há uma tendência em priorizar alvos como o COF e a AMS baseando-se em estudos de neuroimagem no TOC e em montagens promissoras na EMTR (NARAYANASWAMY et al., 2014; MONDINO et al., 2015; D'URSO et al., 2015). Quando o ensaio clínico quase-randomizado apresentado nesta tese foi elaborado, havia apenas o estudo de Volpato e colaboradores (2012), o qual priorizou novamente o CPFDL, que já havia se mostrado ineficaz nos estudos de EMTR.

Apesar de ser um método mais acessível e com efeitos adversos de baixo risco e não duradouros, há alguns desafios a serem cientificamente discutidos que podem comprometer a sua eficácia e o seu uso em ensaios clínicos. Como a ETCC gera uma corrente de baixa intensidade e superficial, apenas 50% dos estímulos atravessam o escalpo e atingem o córtex (NITSCHE et al., 2008). Deste modo, é importante investir em aprimoramentos como melhorar a focalização, o que significa facilitar o fluxo da corrente elétrica na região a ser estimulada e dissipar as correntes na área de referência. Propõe-se a utilização de eletrodos de tamanho reduzido (até $3cm^2$) na região a ser estimulada e eletrodos de referência de tamanho aumentado (até $100cm^2$) (NITSCHE et al., 2007). No ensaio quase-randomizado apresentado neste trabalho, optamos por um eletrodo de $8cm^2$ na AMS e um eletrodo de $40cm^2$ na região supra orbital priorizando este conceito. Outra forma de evitar a estimulação na região do eletrodo de referência é a montagem monocefálica, situando o eletrodo de referência no deltoide esquerdo, por exemplo, (SENÇO et al., 2015; NITSCHE et al.,2008). No entanto, deve-se ter cautela com

esta montagem extra cefálica, pois pode haver um desequilíbrio do sistema nervoso autônomo (NITSCHE et al.,2007).

Outro fator que pode comprometer um ensaio clínico com ETCC é o cegamento. Apesar de em ambos os grupos, ativo e placebo, a corrente percorrer um período de aumento de intensidade gradativo e também de declínio, visando amenizar as sensações provocadas (DA SILVA et al., 2011), os efeitos adversos como vermelhidão e formigamento são mais proeminentes na estimulação real. Quanto maior a intensidade da corrente, mais chance de ocorrerem efeitos colaterais, o que em alguns estudos foi o fator responsável por permitir que os pacientes identificassem a qual grupo pertenciam. A vermelhidão também permite que o pesquisador faça a distinção entre os grupos, prejudicando novamente o cegamento. Uma alternativa proposta para amenizar as sensações de prurido, ardência ou formigamento é o uso de um anestésico local. Contudo, deve-se ter mais precaução com correntes de maior intensidade, porque o efeito anestésico pode mascarar eventos mais sérios como queimaduras na pele (DA SILVA et al., 2011). Uma outra alternativa para evitar o comprometimento do cegamento de um estudo é a redução da intensidade da corrente para 1mA, o que já foi proposto por alguns autores, apesar de não representarem estudos de ETCC no TOC (O'CONELL et al., 2012; MOLIADZE; ANTAL; PAULUS, 2011; GANDINGA; HUMMEL; COHEN, 2006).

Conforme mencionado, o estudo da ETCC no TOC ainda percorre a sua fase inicial. São apenas alguns relatos de caso e, apesar de priorizarem a estimulação do COF e da AMS, ainda há muitas incertezas quanto a melhor montagem e até mesmo uma indefinição quanto ao tipo de estimulo, se excitatório (anódico) ou inibitório (catódico) (D'URSO et al., 2015; MONDINO et al., 2015; HAZARI et al., 2016). Apesar da AMS ser uma área de mais fácil acesso, próximo ao córtex motor primário, a origem da sua hiperatividade não é bem definida (NACHEV; KENNARD; HUSSAIN, 2008). Artigos recentes envolvendo testes de controle inibitório e neuroimagem funcional sugerem a possibilidade da hiperxcitabilidade da AMS ser compensatória (YÜCEL et al., 2007; DE WIT et al., 2010) e fazer parte do endofenótipo do TOC (DE WIT et al., 2012). Os relatos de caso publicados até o presente mostram resultados promissores com a utilização de ânodo na AMS (NARAYANASWAMY et al., 2014), como também a utilização de cátodo na AMS (D'URSO et al., 2015). Estes dados corroboram com a necessidade de investir-se em ensaios clínicos controlados-randomizados, como o estudo preliminar apresentado na tese.

Como perspectivas futuras, pode-se almejar a utilização dos métodos não-invasivos de estimulação, como terapia adjuvante à farmacoterapia e terapias cognitivo-comportamentais. Para tanto, muitos avanços parecem ser necessários: em relação à EMTR e à ETCC, o

desenvolvimento de novas técnicas de cegamento para melhorar a qualidade de estudos duplo-cegos controlados-randomizados são fundamentais; outro ponto importante, também limitador destas técnicas, é a precisão do posicionamento dos alvos. Para tanto, incentiva-se o uso da neuronavegação, com auxílio da neuroimagem. Vale ressaltar ainda que da mesma forma que os estudos com a ECP provaram a necessidade de prolongar o período de estimulação por meses ou anos, a fim de encontrar resultados satisfatórios na redução dos sintomas obsessivos-compulsivos, (GREENBERG; RAUCH; HABER, 2010), estudos futuros com EMTR e ETCC devem priorizar intervenções a longo prazo. Por último, é de suma importância a manutenção de pesquisas voltadas para a fisiopatologia do TOC e, provavelmente, elucidar a relação da hiperexcitabilidade da AMS no mecanismo da doença.

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APÊNDICE – THE MANAGEMENT OF DELIRIOUS MANIA IN AN INTENSIVE CARE UNIT: A REASON FOR ADMISSION, ONE POTENTIAL COMPLICATION AND A PROPOSED SOLUTION.

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CASE REPORT

The management of delirious mania in an intensive care unit: a reason for admission, one potential complication and a proposed solution

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A patient with delirious mania was treated with high dose intramuscular antipsychotics and anticholinergics resulting in severe Ogilvie syndrome, admission to an intensive care unit (ICU), and initial management with dexmedetomidine. Eventually, she was successfully treated with electroconvulsive therapy within ICU.

Key words: delirious mania; critical care; Ogilvie syndrome; dexmedetomidine; catatonia; electroconvulsive therapy

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Declaration of interest: None

Introduction

Delirious mania is a severe but under-recognised syndrome characterised by altered consciousness and disorientation typical of delirium and excitement, grandiosity, emotional lability and insomnia characteristic of mania (Fink, 1999). It is typically not due to drug use, general medical conditions or neurologic illness (Jacobowski et al. 2013). Sudden onset, incontinence and inappropriate toiletting in a patient using inadequate (or no) clothing are distinctive features of the syndrome (Karmacharya et al. 2008). While initially believed to be rare, recent reports suggest that delirious mania may be present in up to 25% of all cases of acute mania (Fink, 1999). Indeed, when this condition is not recognised or improperly treated, it often progresses hastily and can become life threatening (Jacobowski et al. 2013). In this report, we describe a case of delirious mania partly managed in an intensive care unit (ICU) and its malignant, yet favourable, course.

Case report

Mrs A, a 61 year-old widow with a lifelong history of bipolar II disorder, was kept euthymic during the last year with quetiapine (700 mg/day), lithium (450 mg/day (plasma levels = 0.7 meq/L)) and clonazepam (2 mg/day). Her last major depressive episode remitted almost a year previously, after treatment with desvenlafaxine (50 mg/day), which was withdrawn a few weeks after remission. Retrospectively, we were able to identify periods of irritability, circumstantiality and excessive involvement in pleasurable activities. Lately, however, after showing protracted hypomanic symptoms for a more than a month, and despite the addition of haloperidol 10 mg/day to her drug scheme, Mrs A exhibited the sudden onset of a severe episode of mixed confusional and manic symptoms, which culminated in an admission to a closed psychiatric facility with an ICD-10 diagnosis of F31.2 (bipolar affective disorder, current episode manic with psychotic symptoms).

Despite two bilateral brief-pulse ECT sessions on alternating days, escalating excitement lead to the administration of high dose intramuscular antipsychotics (including haloperidol, zuclopenthixol and olanzapine) and anticholinergics (prometazine) by staff on call. Subsequently, the patient developed abdominal distension with no passage of flatus and stool, and absent peristalsis. Abdominal CT disclosed small and large bowel gas distension and mechanical causes were excluded. This pattern was consistent with the diagnosis of Ogilvie syndrome (K56.6). Eventually, Mrs A was admitted to an ICU.

At that time, antipsychotics were interrupted, constipation was treated conservatively, and Mrs A's disturbed mental status was initially managed with dexmedetomidine administered by continuous infusion for more than a week by ICU staff. Following the recommendation of her assisting psychiatrist, who believed that no evidence supported the use of this drug as an effective treatment for acute mania, ECT was resumed and three additional bilateral sessions, on alternating days, were safely prescribed during dexmedetomidine administration.

Despite short-term control of agitation, drug-related side effects (i.e. hypotension and bradychardia) and concerns over the development of tolerance lead to dexmedetomidine discontinuation, resulting in severe and persistent catatonic symptoms, such as rigidity, negativism/mutism, stereotypies, grasping, echolalia and echopraxia. At that point, due to increased severity of the psychiatric picture, three bilateral ECT sessions were employed on consecutive days and high dose lorazepam (8 mg/day) was started. The patient was kept on the ICU until her medical status improved substantially and allowed treatment continuation in a psychiatric unit (Fig. 1).

Discussion

Our patient exhibited Ogilvie syndrome as a complication of the repeated administration of intramuscular antipsychotics with and without accompanying anticholinergics. Ogilvie syndrome is a condition that can result in bowel ischemia or perforation in 3%–15% of patients, with a 50% reported mortality rate (Hsu et al. 2011). It is reported to be among the leading causes of death in patients treated with clozapine, the most potent anticholinergic drug among antipsychotics (Palmer et al. 2008). While conservative treatment of Ogilvie syndrome usually involves bowel rest (nothing by mouth), nasogastric/colonic decompression and correction of electrolytes disturbances, refractory cases are managed with neostigmine, cecostomy or colectomy. Fortunately, our patient was successfully managed in an ICU with a conservative treatment approach and the withdrawal of antipsychotics and anticholinergics (Hsu et al. 2011).

In the ICU, the delirious mania was initially managed with continuous infusion of dexmedetomidine, a potent alpha 2 agonist that significantly reduces noradrenergic tonus (Carollo et al. 2008). Although widely used for procedure sedation in ICU, we are not aware of any previous attempt to employ dexmedetomidine in the treatment of primary psychiatric disorders. Nevertheless, there are earlier reports of dexmedetomidine being used to manage post-ECT agitation (Cohen and Stewart, 2013; Bryson et al. 2013; O'Brien et al. 2010; Mizrak et al. 2009) and to sedate manic patients during surgical procedures (Ackerman & Mount, 2011). Unfortunately though, it is unclear whether dexmedetomidine can be employed on a regular basis (i.e. more than a week) to treat acute mania. Therefore, as indicated (Nicolato et al. 2009), three additional bilateral ECT sessions on alternating days had to be added to Mrs A's treatment regimen at that point, with meagre response.

In addition to a lack of evidence regarding efficacy, the administration of dexmedetomidine was associated with hypotension and bradychardia. Also, concerns that continuous use of dexmedetomidine may result in tachyphylaxis (diminished response) lead to its discontinuation after one week, with resulting severe and persistent catatonia. It is unclear whether catatonia was a manifestation of delirious mania or dexmedetomide withdrawal. However, it has been demonstrated that sudden interruption of dexmedetomidine may lead to sympathetic over-activity, including tachycardia, hypertension and agitation (Kukoyi et al. 2013). Although catatonic symptoms have been reported in delirious mania cases such as ours (Detweiler et al. 2009; Lee et al. 2012), they are also seen in benzodiazepines (Amos, 2012), hypnotics (Hsieh et al. 2011), gabapentin (Rosebush et al. 1999) and alcohol (Geoffroy et al. 2012) withdrawal, a phenomenon thought

DM: delirious mania; OSY: Ogilvie syndrome; CAT: catatonia; QTP: quetiapine (up to 500 mg/day); HLP: haloperidol (up to 20 mg/day); PMT: prometazine (up to 25 mg/day); PRN: different intramuscular antipsychotics administered on alternate days, including: (i) Haloperidol (up to 10 mg/day) w/ or w/out Prometazine (up to 50 mg/day), (ii) Zuclophentixol (up to 50 mg/day), and (iii) Olanzapine (up to 5 mg/day); DMD: dexmedetomidine (up to 70 mcg/hr); LZP: lorazepam (up to 8 mg/day); ECT: electroconvulsive therapy.

Fig. 1. Longitudinal relationships between clinical conditions and therapeutic approaches adopted in the case of Mrs A.

to support the involvement of decreased GABA activity in the pathophysiology of catatonia.

Due to increased severity of symptoms after dexemedetomidine withdrawal, three bilateral ECT sessions were employed on consecutive days and high dose lorazepam was started. In fact, while some authors have discouraged the use of daily ECT due to increased rates of cognitive dysfunction (Mukherjee et al. 1994), other experts have argued that it may result in faster therapeutic responses (van Waarde et al. 2010), thus being desirable in situations where life threatening conditions, such as delirious mania, are present (Fink & Taylor, 2003). After three ECT daily sessions, our patient was discharged and continued treatment in a closed psychiatric facility. Eventually, a total of 11 bilateral ECT sessions were administered, leading to a substantial improvement of delirious mania and allowing treatment follow-up on an outpatient basis.

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ANEXO 1 –YALE-BROWN OBSESSIVE-COMPULSIVE CHALLENGE SCALE (YBOCCS) (PATIENT-RATED)

Name: _____ Date: _____ Time: _____ Elapsed Time: _____

RATE OVER TIME LAST 60 MINUTES INCLUDING NOW. Please discuss the definitions of “obsessions” and “compulsions” with your clinician. Place a vertical mark on line corresponding to severity of your symptoms. For example:

	None	Mild	Moderate	Severe	Extreme
	0	**1**	**2**	**3**	**4**
1. Time spent on obsessive thoughts.	|_____|_____|_____|_____|				

	None	Mild	Moderate	Severe	Extreme
	0	1	2	3	4
1. Time spent on obsessive thoughts.	|_____|_____|_____|_____|				

	None	Mild	Moderate	Severe	Extreme
	0	1	2	3	4
2. Anxiety due to obsessive thoughts.	|_____|_____|_____|_____|				

	None	Mild	Moderate	Severe	Extreme
	0	1	2	3	4
3. Time spent performing compulsive behaviors.	|_____|_____|_____|_____|				

	None	Mild	Moderate	Severe	Extreme
	0	1	2	3	4
4. Intensity to compulsions to perform the behavior.	|_____|_____|_____|_____|				

	Complete control	Mild	Moderate	Severe	Extreme
	0	1	2	3	4
5. Degree of indecisiveness. (Difficulty in choosing between simple alternatives)	|_____|_____|_____|_____|				

	None	Mild	Moderate	Severe	Extreme
	0	1	2	3	4
6. Guilty (certain that did, or will do, something terrible or wrong.	|_____|_____|_____|_____|				

	Complete control	Much	Moderate	Little	No Control
	0	1	2	3	4
7. Degree of control over obsessive thoughts and/or compulsive behavior.	|_____|_____|_____|_____|				

	Certain won’t happen	Unlikely	Not Sure	Likely	Certain will happen
	0	1	2	3	4
8. Conviction that something awful will happen unless behavior performed.	|_____|_____|_____|_____|				

	None	Mild	Moderate	Severe	Extreme
	0	1	2	3	4
9. Overall severity of obsessions.	|_____|_____|_____|_____|				

	None	Mild	Moderate	Severe	Extreme
	0	1	2	3	4
10. Overall severity of compulsions.	|_____|_____|_____|_____|				

ANEXO 2 –ESCALA DE DESAFIO OBSESSIVO-COMPULSIVO DE YALE-BROWN (YBOCCS) (PATIENT-RATED)

Name: _____ Date: _____

RATE OVER TIME LAST 60 MINUTES INCLUDING NOW. Please discuss the definitions of “obsessions” and “compulsions” with your clinician. Place a vertical mark on line corresponding to severity of your symptoms. For example:

	Nenhum	Leve	Moderado	Grave	Extremo
	0	1	2	3	4
1. Tempo gasto com os pensamentos obsessivos	|_____|	|_____|	|_____|	|_____|	|_____|

	Nenhum	Leve	Moderado	Grave	Extremo
	0	1	2	3	4
1. Tempo gasto com os pensamentos obsessivos	|_____|	|_____|	|_____|	|_____|	|_____|

	Nenhum	Leve	Moderado	Grave	Extremo
	0	1	2	3	4
2. Ansiedade em consequência aos pensamentos.	|_____|	|_____|	|_____|	|_____|	|_____|

obsessivos.

	Nenhum	Leve	Moderado	Grave	Extremo
	0	1	2	3	4
3.Tempo gasto realizando os rituais**.**	|_____|	|_____|	|_____|	|_____|	|_____|

(caso se aplique rituais mentais)

	Nenhum	Leve	Moderado	Grave	Extremo
	0	1	2	3	4
4. Vontade de realizar um ritual.	|_____|	|_____|	|_____|	|_____|	|_____|

	Nenhum	Leve	Moderado	Grave	Extremo
	0	1	2	3	4
5. Grau de indecisão (Dificuldade para escolher entre alternativas simples	|_____|	|_____|	|_____|	|_____|	|_____|

	Nenhum	Leve	Moderado	Grave	Extremo
	0	1	2	3	4
6. -Culpa (Preocupado com ter feito ou que fará algo horrível ou errado)	|_____|	|_____|	|_____|	|_____|	|_____|

	Completo	Muito	Moderado	Pouco	Nenhum
	0	1	2	3	4
7. Grau de controle em relação aos pensamentos e/ou aos rituais compulsivos	|_____|	|_____|	|_____|	|_____|	|_____|

	Certamente não acontecerá	Improvável	Não tenho certeza	Provavelmente	Irá acontecer
	0	1	2	3	4
8 Convicção de que algo terrível irá acontecer ao menos que . um determinado ritual seja realizado	|_____|	|_____|	|_____|	|_____|	|_____|

	Nenhum	Leve	Moderado	Gravee	Extremo
	0	1	2	3	4
9. Gravidade global das obsessões.	|_____|	|_____|	|_____|	|_____|	|_____|

	Nenhum	Leve	Moderado	Grave	Extremo
	0	1	2	3	4
10. Gravidade global das compulsões.	|_____|	|_____|	|_____|	|_____|	|_____|