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Psychotherapy and psychopharmacology utilization following repetitive transcranial magnetic stimulation (rTMS) in patients with major depressive disorder

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ABSTRACT

Lifetime prevalence of major depressive disorder (MDD) among a sample of adults in the United States has been reported as over 16%. Repetitive transcranial magnetic stimulation (rTMS) has become a treatment option for a subset of treatment-refractory patients with MDD. In a population of 159 commercial health plan individuals, we used claims data to compare utilization of antidepressants, antipsychotics, and psychotherapy during the one-year time period prior to rTMS initiation to the one-year time period starting 60 days after rTMS initiation. Both antidepressant and antipsychotic use declined significantly from three months pre-rTMS compared to each of four quarterly post-rTMS time points. Psychotherapy utilization also significantly declined post-rTMS compared to pre-rTMS. The reduction in medication utilization could reflect clinical improvement of the study population, and the absence of even greater reductions in utilization likely reflects the lack of clinical guidelines for antidepressant prescribing in the aftermath of rTMS treatment.

1. Introduction

Lifetime prevalence of major depressive disorder (MDD) among a sample of adults in the United States has been reported as 16.2% (Kessler et al., 2003). Standard treatments for MDD include psychotherapy, pharmacotherapy, and/or electroconvulsive therapy (ECT). Although many individuals respond to standard treatments for depression, some do not benefit or cannot tolerate these interventions. Therefore, alternate treatment options have been investigated, including high frequency repetitive transcranial magnetic stimulation (rTMS), vagal nerve stimulation and cranial electrical stimulation (Miniussi et al., 2005).

Based on the principle of electromagnetic induction, TMS modulates the brain's electrical environment using magnetic fields, which pass through the scalp and skull unimpeded. These fields are produced by passing rapidly alternating electrical currents through a coil with a ferromagnetic core (eg, an electromagnet in lieu of a permanent magnet). The magnetic field strength produced by TMS varies from 1.5 to 3 T and is comparable to an MRI device, except that it focuses on a limited area of the cortex using a circular, figure-eight, conical, or helmet-like coil design (eg, H-coil). TMS can be administered in single pulses or as a brief series of pulses, called a train, for research, diagnostic, and therapeutic purposes. When used clinically, several thousand pulses are usually applied over a period of minutes to hours. This is called repetitive transcranial magnetic stimulation or "rTMS". rTMS is less invasive than vagal nerve stimulation, and is not intended to induce seizures like electroconvulsive therapy (ECT). rTMS may cause some short-term side effects such as headache, tingling of facial muscles, scalp discomfort, lightheadedness, or discomfort from the noise that the device makes. Hearing loss and seizures have been reported as uncommon side effects. Although symptom relief may not take place for several weeks (Bersani et al., 2013), a meta-analysis of twenty-nine randomized controlled trials of rTMS has shown efficacy compared to placebo treatment after approximately thirteen sessions (Berlim et al., 2014). rTMS studies have generally included patients whose major depression has been refractory to at least one or two antidepressant trials. Among such patients, rTMS is now considered first line therapy with a high level of evidence (Milev et al., 2016). In a 2014 review of nine studies comprising 425 individuals, rTMS outcomes were reported to be similar to electroconvulsive therapy (ECT) but with fewer side effects; however, ECT was found to be more effective in persons with concomitant psychosis (Ren et al., 2014). The study was published

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following a 2013 meta-analysis of seven randomized trials comprising 294 individuals, which concluded that ECT was more effective than rTMS (Berlim et al., 2013). Other evidence suggested rTMS to be superior to sham treatment (Berlim et al., 2014) and rTMS became an established treatment option for a subset of patients with MDD. Accordingly in April 2016, Cigna[1], a health services company, began authorizing coverage for initial courses of rTMS as a medically necessary treatment for adult patients with MDD (Cigna, 2018), as described in the *Methods* section below.

Despite prior studies of treatment efficacy, we are unaware of observational studies focused on the extent of psychotherapy or pharmacotherapy utilization upon completion of a course of rTMS. The Clinical TMS Society, while offering recommendations on tapering of rTMS, reintroducing of rTMS in the event of a depression relapse, and using rTMS with concurrent pharmacotherapy, does not provide guidance on discontinuing concomitant medications or psychotherapy after a course of rTMS has been completed (Perera et al., 2016). The current observational study considers rTMS patients in a commercial health plan population as their own controls to elucidate real-world practice patterns and utilization in the absence of clear evidence-based clinical practice guidelines. We compare a baseline of the one-year time period prior to initiation of rTMS with the one-year time period starting 60 days after rTMS initiation, assessing changes in the number of psychotherapy sessions, number of different antidepressants used, and number of different antipsychotics used.

2. Methods

2.1. Subjects

The study population consisted of 159 commercial health plan members who received rTMS starting between April 1, 2016 and March 31, 2017. To be included, individuals were required to have medical, behavioral and pharmacy benefit coverage during the full timeframe of review, be at least 18 years of age and also under 65 years of age. Members who received rTMS had to meet all of the following three criteria: (1) previously attempted at least three trials of antidepressant medications at adequate therapeutic doses from at least two different classes of antidepressant medications for at least four weeks, and/or had been unable to complete an adequate medication trial due to intolerance to a particular medication or class of medication; (2) experienced no significant reduction in depressive symptoms following pharmacotherapy as documented by validated depression monitoring scales; and (3) had received an adequate trial of an evidence-based psychotherapy known to be effective in the treatment of major depressive disorder, without significant improvement in depressive symptoms, as documented by validated depression monitoring scales.

2.2. Procedures

Using claims data, utilization of antidepressants, antipsychotics and psychotherapy was compared for individuals for one year prior to rTMS initiation versus a one-year period starting 60 days after rTMS initiation, with the presumption that rTMS itself occurred over 60 days. The approximate time course of rTMS was determined based on our experience with provider-generated CPT® billing codes (American Medical Association, 2018), specifically 90867, 90868 and 90869 which are uniquely used for billing rTMS as opposed to other types of TMS treatment. Typically, the initial rTMS treatment which includes cortical mapping, motor threshold determination, delivery and management (90867) was billed only once. Subsequent motor threshold redetermination with delivery and management (90869) was billed from one to three times, and subsequent rTMS delivery and management (90868) was billed for the remaining sessions, generally about thirty-three in number.

Accordingly, claims for Cigna pharmacy medications and Cigna behavioral health claims for psychotherapy utilization were compared from one year (365 days) prior to beginning rTMS to the one year (365 days) period beginning 60 days after the first rTMS treatment. Additional service codes included the following: individual psychotherapy (CPT: 90832, 90834, 90837); psychotherapy with patient and/or family when performed with evaluation and management service (CPT: 90833, 90836, 90838); group psychotherapy (CPT: 90853); family psychotherapy (CPT: 90846, 90847). For antidepressants and antipsychotics, prescription fill dates and the number of days supplied (e.g. 30 days) were used to determine how many unique medications were on board at each time point assessed during the study period, namely three, six, nine, and twelve months before and after the rTMS 60-day treatment period. Sustained and extended release versions of agents, e.g. bupropion, was considered to be the same medication as the regular release formulation such that only pharmacologically distinct agents were counted at each time point.

2.3. Data analysis

Psychotherapy visits were computed on an annual basis during the pre- and post-rTMS 60-day treatment period. Antidepressant and antipsychotic utilization was counted at quarterly intervals for each individual as noted above. Data were compiled and analyzed using SAS software, Version 9 of the SAS System, copyright ©2013 SAS Institute Inc. Pre- versus post-rTMS comparisons were evaluated with a signed rank test.

3. Results

From April 1, 2016 through March 31, 2017, 534 individuals were identified as having received health plan authorization for rTMS treatment and a resulting course of rTMS coordinated with their physicians. Of these, 159 had medical, behavioral, and pharmacy benefits for the entirety of the study period and were therefore eligible for inclusion. Of the 159, 86 (54%) were female, average age was 44.4 years (standard deviation = ± 13.3 years), and 86% were Caucasian.

We first reviewed the 159 individuals who received some form of psychotherapy during the one-year pre-rTMS period shown in Table 1. Of these individuals, 91 were billed an individual psychotherapy code, for an average of 16.76 visits (standard deviation = ± 16.34) in the pre-rTMS period, compared to an average of 13.96 visits (standard deviation = ± 17.59) during the one-year post-rTMS period, which was a 17% decline in visits ($p = 0.0083$). There were 63 patients billed for psychotherapy, either individually or with family, coded as part of medical evaluation and management, i.e. provided by a prescribing clinician. There were, on average, 6.38 such visits (standard deviation = ± 7.29) in the pre-rTMS period and 5.02 visits (standard deviation = ± 8.99) in the post-rTMS period, a 21% decline. This decline was also statistically significant ($p = 0.0109$).

We next evaluated antidepressant and antipsychotic usage among rTMS recipients. Of 159 individuals in the study, 149 individuals were prescribed antidepressants at some point during the study; 146 individuals (92% of the study population) were prescribed an antidepressant at some point during the one-year pre-rTMS period, and 128 individuals (81% of the study population) were prescribed an antidepressant during the post-period. Quarterly antidepressant averages per individual are shown in Fig. 1. The average number of different antidepressants per individual generally increased in the months leading up to the onset of rTMS, peaking at the 6 month pre-period (1.54, standard deviation = ± 1.09), before tapering off slightly to 1.49, (standard deviation = ± 0.98) three months pre-rTMS. Post-

[1] The term "Cigna" as used herein refers to operating subsidiaries of Cigna Corporation including Cigna Health and Life Insurance Company and Cigna Behavioral Health, Inc.

Table 1
Comparison of pre-post rTMS time periods for psychotherapy visits.

	N	Pre period average visits	Post period average visits	Difference	% Difference	*P*-value
Individual psychotherapy	91	16.76	13.96	2.80	−17%	0.0083
Psychotherapy	63	6.38	5.02	1.36	−21%	0.0109

Notes: rTMS = repetitive transcranial magnetic stimulation. Comparison includes customers who had a visit in the pre period. Data were capped at the 95th percentile. Psychotherapy visits shown on the second row were with patient and/or family when performed with evaluation and management service.

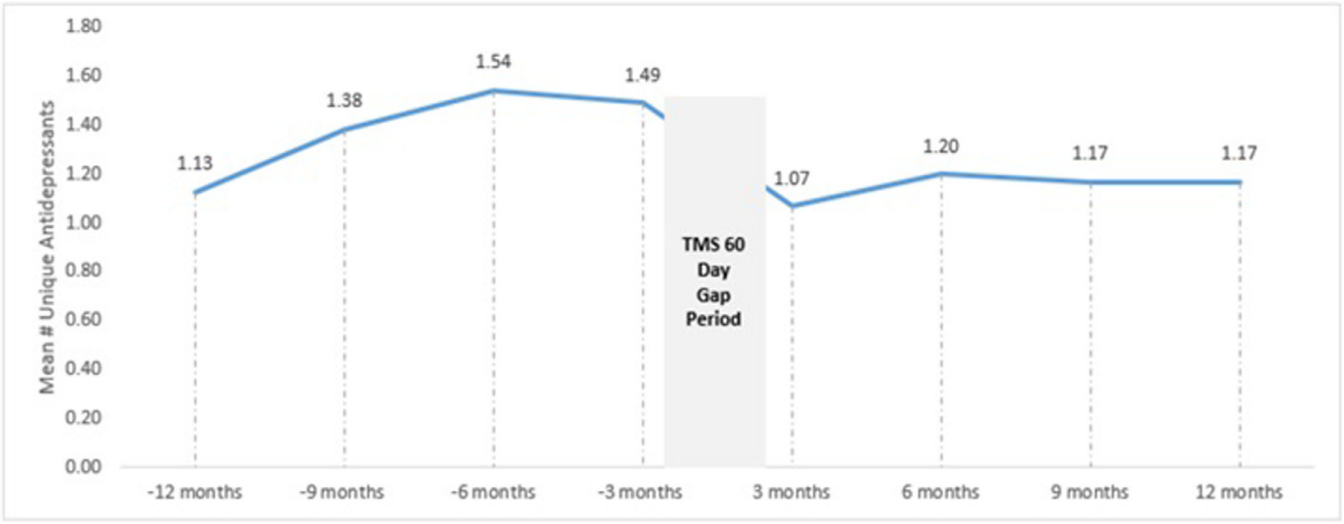

Fig. 1. Quarterly antidepressant averages per individual.

Table 2
Mean difference in antidepressants.

Antidepressants	Mean	Difference	*P*-value
Comparison of 3 months prior to TMS to:	1.49	N/A	N/A
3 months post	1.07	Mean diff: 0.42 Std dev: 1.05	<0.0001
6 months post	1.20	Mean diff: 0.29 Std dev: 1.12	0.0027
9 months post	1.17	Mean diff: 0.32 Std dev: 1.09	0.0003
12 months post	1.17	Mean diff: 0.32 Std dev: 1.09	0.0004

rTMS, the average number of antidepressants per subject at quarterly time points dropped to an average of 1.07, (standard deviation = ± 0.87) at the 3 month post-rTMS and then slightly increased to 1.17 in the 9 and 12 month post-rTMS (standard deviation = ± 0.83, standard deviation = ± 0.78, respectively), with all values being highly statistically significant when compared with the three months pre-rTMS value of 1.49 (p-values from <0.0001 to 0.0027) shown in Table 2.

Of 159 individuals in the study, 92 were prescribed antipsychotics at some point during the study; 77 (48%) in the pre-rTMS period compared to 61 individuals (38%) in the post-rTMS period. Similarly (Fig. 2), antipsychotic use increased over time in the pre-rTMS period, monotonically from 0.51 (standard deviation = ± 0.60) to 0.80 (standard deviation = ± 0.63). By contrast, post-rTMS, the number of antipsychotics ranged from 0.51 (standard deviation = ± 0.60) to 0.61 (standard deviation = ± 0.63) with all differences from the 3 month pre-rTMS value of 0.80 being statistically significant (p-values from 0.0006 to 0.0110) shown in Table 3.

4. Discussion

In a commercial health plan population of adults diagnosed with MDD, we used claims data to assess statistically and/or clinically significant changes in psychotherapy and medication utilization during one year following the 60 days after rTMS initiation, compared to the year prior to rTMS. We found statistically significant reductions in utilization of different antidepressants and antipsychotics and in psychotherapy visits, either individually or with family.

Although this observational study of utilization based on claims data did not access medical records such that we could directly assess clinical improvement, it is certainly plausible and our strong hope that the decrease in medication usage and psychotherapy visits represents at least modest and sustained clinical improvement after rTMS. Of the 159 individuals who received rTMS during the study period, only twelve received additional rTMS sessions after the initial course. These additional sessions started between 157 days later to 352 days later, for an average start date of over 8.5 months after the initial course. Further support of clinical improvement is the stability of the post-rTMS average number of antidepressants prescribed at 3-month intervals, ranging from 1.07 to 1.20 at each of the three-month intervals, a finding that would presumably have been less likely if a larger proportion of the sample relapsed and perhaps been prescribed additional medications. That said, a larger drop in the number of antidepressants in the year following rTMS would have been even more suggestive of robust clinical improvement.

While a standard course of rTMS has shown efficacy in treating MDD, the durability of the response remains unclear due to the short-term follow-up period of most studies, and has been shown to attenuate to the point of relapse even in studies involving maintenance or booster rTMS sessions after the initial course (Guo et al., 2017). Thus, the absence of further declines in medication utilization over the course of a year post-rTMS may reflect the combination of both remission among some individuals who were taking even fewer medications after rTMS and relapse among other individuals who were taking more. In support of this interpretation of our findings is that third-party reimbursement for rTMS is typically available only after three or more different antidepressants have been previously failed or not tolerated by patients

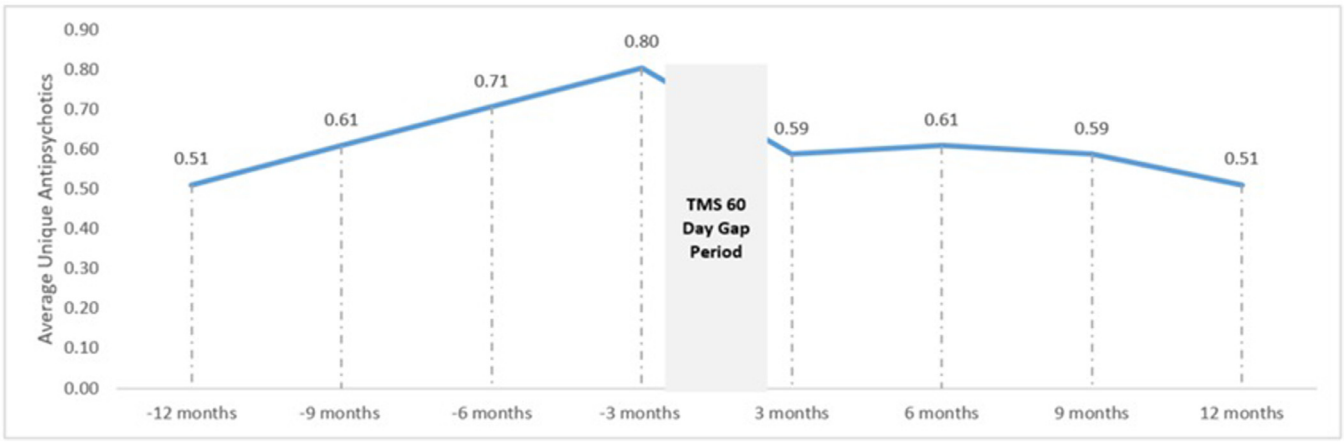

Fig. 2. Quarterly antidepsychotic averages per individual.

Table 3
Mean difference in antipsychotics.

Antipsychotics	Mean	Difference	*P*-value
Comparison of 3 months prior to TMS to:	0.80	N/A	N/A
3 months post	0.59	Mean diff: 0.22 Std dev: 0.81	0.0110
6 months post	0.61	Mean diff: 0.20 Std dev: 0.73	0.0106
9 months post	0.59	Mean diff: 0.22 Std dev: 0.80	0.0096
12 months post	0.51	Mean diff: 0.29 Std dev: 0.81	0.0006

(Aetna, 2018; Anthem, 2018), suggesting a greater degree of pre-existing treatment refractoriness in these patients, and as such, a greater potential to relapse after treatment. Additionally, it is possible that individuals with a relapse may have paid out of pocket for additional rTMS treatments that would not be accounted for in our claims data, or for injectable medication (i.e. ketamine) that is reimbursed through one's medical benefit rather than the pharmacy benefit.

Further reductions in medication utilization may also reflect lack of clinical guidelines around tapering or discontinuation of other depression treatments following clinical response to rTMS. In fact, the Clinical TMS Society's (CTMS) Consensus Review and Treatment Recommendations for TMS Therapy for Major Depressive Disorder concerning TMS continuation or maintenance for patients who benefit from an acute course, states simply, "A majority of CTMS' members use maintenance medications and psychotherapy, considering continuation or maintenance TMS therapy when other established methods of maintenance antidepressant therapy fail to provide a satisfactory sustained pattern of clinical benefit or a patient has a history of frequent relapse (two or more in one year)" (Perera et al., 2016). While certainly the role of maintenance psychotherapy and medication in the treatment of MDD has been well established regardless of whether rTMS was used, such maintenance therapy is not universally indicated. Its use has been recommended by the *American Psychiatric Association's Practice Guideline for the Treatment of Patients with Major Depressive Disorder, Third Edition* specifically for patients "who have had three or more prior major depressive episodes or who have chronic major depressive disorder," or who have additional risk factors for recurrence. In our sample of rTMS recipients, many individuals may have had chronic depression or a longstanding history of depressive episodes such that maintenance therapy would have been indicated without rTMS treatment. However, it is certainly conceivable that many individuals received rTMS for an initial depressive episode, rather than a chronic course, due to insufficient response to or intolerance of psychotherapy and prior pharmacological treatment. Because our study captured treatment based on claims data for just one year prior to rTMS, we were not able to determine how many individuals had chronic depression or multiple, prior depressive episodes that would indicate the need for maintenance therapy. Furthermore, due to turnover of individuals who enter or exit their benefit plans, it is often impossible to capture claims indicating long-term treatment. That said, our study seems to support the CTMSs statement that medication and psychotherapy maintenance therapy is the norm among recipients of rTMS, though we know of no clinical guidelines or empirical evidence for this practice. Given the side effect profile of many medications, not to mention the time and cost involved in both medication and psychotherapy treatment, our study strongly suggests the need for further evaluation of when treatment with these modalities can safely be tapered and discontinued, rather than maintained, among patients with a time-limited history of MDD who respond well to rTMS.

Our study had several limitations. This study was based on administrative claims data from a commercial health plan, thus it was limited to prescriptions filled via Cigna pharmacy. We were not able to provide direct clinical correlation from providers or from patients; therefore, we cannot determine, for example, how effective a course of rTMS may have been as measured by depression scores. Secondly, our study was limited in time to one year before and after a 60-day time period allotted for rTMS treatment, so, as noted above, we cannot make inferences about the long-term course of depression endured by rTMS recipients. A quasi-experimental design such as this one is unable to prove causality, so we cannot state definitively that the reduction in antidepressants, antipsychotics and psychotherapy visits after rTMS was directly related to this treatment. However, because our main purpose was to observe utilization patterns after rTMS, particularly psycho-pharmacologically, our study may paint an accurate picture of clinical practice among health plan patients with treatment-refractory major depressive disorder.

Authors' disclosures

All authors were employees of Cigna Health and Life Insurance Company.

Conflict of interest

The authors declare no conflicts of interest associated with this research study.

CRediT authorship contribution statement

Priya Needs: Investigation, Writing - review & editing, Conceptualization, Data curation, Writing - original draft. **Stephanie D.**

Mote: Investigation, Writing - review & editing, Data curation. **Michael Manocchia:** Investigation, Writing - review & editing, Data curation. **Jeffrey D. King:** Investigation, Writing - review & editing. **Debra D. Szuba:** Investigation, Writing - review & editing, Writing - original draft. **Stuart L. Lustig:** Investigation, Writing - review & editing, Conceptualization, Writing - original draft. **Vikram N. Shah:** Investigation, Writing - review & editing, Writing - original draft.

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Ethics

This project was undertaken as a Quality Improvement initiative and as such does not constitute human subjects research in accordance with Office of Human Research Protections guidance on Health and Human Services regulations at 45 CFR 46.102(d). The analytic protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.05.020.

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