treatment of major depression, and capitalizing upon a patient's social networks should become a priority.

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DOI:10.1002/wps.20296

New analytic strategies help answer the controversial question of whether alliance is therapeutic in itself

The association between alliance (at a given point in time or aggregated across several sessions) and outcome is one of the most consistent findings in psychotherapy research[1,2]. However, the mechanism underlying this association is one of the most controversial. Some theorists and researchers believe that alliance is therapeutic in itself; others argue that it is a by-product of effective treatment or of a trait-like patient ability to benefit from treatment[3,4]. For many years, the debate has been confined mainly to the domain of theory. Recently, several studies have applied advanced analytic strategies to explore the mechanism behind the alliance-outcome association.

The argument that alliance is simply a by-product of successful treatment has been previously addressed by studies controlling for early symptomatic change when examining the ability of alliance to predict outcome. Some of these studies suggest that alliance is indeed a by-product of early symptomatic change, while others indicate that it can predict outcome even after controlling for that change[1]. However, previous studies treated alliance as a static variable, and ignored the fact it can change across treatment, which may have contributed to the mixed results. Recent studies used statistical methods such as autoregressive cross-lagged modeling to examine whether alliance levels precede symptomatic levels, session by session over the entire course of treatment. The findings show that alliance indeed precedes symptom reduction over the course of treatment in both psychotherapy[5-7] and psychopharmacotherapy[8], suggesting that it is a true predictor of outcome.

The other challenge to the argument that alliance is therapeutic is the proposition that alliance is a by-product of a patient's general trait-like ability to benefit from treatment. Individuals who are more capable of forming strong and satisfying relationships with others may also have a better chance of forming a strong and satisfying alliance with their therapist. Alliance cannot be said to be therapeutic in itself if it is a trait-like characteristic of the patient. Recently developed detrending and centering methods[9] have made it possible to explore empirically the theoretical distinction between the state-like and trait-like components of alliance and determine which of the two predicts outcome. Studies show that patients' pre-treatment interpersonal characteristics can predict alliance as it develops across treatment[10] and that the alliance trait-like component can significantly predict outcome[7,11]. However, studies also suggest that state-like changes in alliance over treatment can have a significant effect on outcome[5,7,11].

If state-like changes in alliance can bring about therapeutic change, manipulating these characteristics is expected to influence outcome. One recent study has examined this question empirically, randomizing patients to either a feedback condition, in which therapists received feedback on the alliance to assist them in strengthening its state-like component, or to a control condition in which no feedback was provided. The study found a greater effect of the state-like component of alliance on outcome in the feedback condition[7], suggesting that the effect of this component of alliance on outcome can indeed be manipulated. Furthermore, another recent study suggests that when therapists detect poor alliance with their patients, and have sufficient time to work on strengthening the state-like component of alliance, this component is associated with a better outcome[12].

The groundbreaking methodologies recently applied in psychotherapy research bring new insights to our understanding of the question of whether alliance is therapeutic. These methodologies are poised to play a critical role in future research, focusing on diverse populations and therapeutic orientations,

and may lead to the development of even more advanced models of moderation-mediation analyses.

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DOI:10.1002/wps.20305

Clinical efficacy and safety of repetitive transcranial magnetic stimulation in acute bipolar depression

Though bipolar disorder is characterized by episodes of mania/hypomania, depressive episodes pose the most burden for patients suffering from the disorder. Regrettably, few proven treatments exist for bipolar depression, and many patients either do not respond to, or have difficulty tolerating these treatments. Hence, novel, safe and effective treatments are urgently needed.

The neuromodulatory approaches, such as repetitive transcranial magnetic stimulation (rTMS), have been demonstrated to be efficacious in randomized double-blind sham-controlled trials (RCTs) in treating depressive episodes in patients with major depressive disorder. However, it is unclear whether the antidepressant efficacy of rTMS extends to bipolar depression. Many RCTs of rTMS in major depression have included patients with bipolar depression. Therefore, our objective was to systematically review the rTMS literature to identify bipolar patients included in randomized trials in order to synthesize the data on clinical efficacy and safety of rTMS in bipolar depression.

We registered the literature review protocol with PROSPERO (CRD#42015017089), which involved considering systematic reviews of rTMS in major depression and searching English-language publications in MEDLINE, EMBASE, and CENTRAL until July 11, 2015. We included randomized, double-blind, sham-controlled trials of rTMS involving $\geq$5 sessions that randomized patients with bipolar depression to both active and sham rTMS arms. We excluded RCTs that did not include patients with bipolar disorder, and those for which rates of clinical response were not reported or could not be obtained in correspondence with the investigators. We synthesized the data using Comprehensive Meta-Analyses Version 2.0 (Biostat, Englewood, NJ, USA). We analyzed intention to treat data with random effects models. Efficacy was investigated by risk difference (RD) and the number needed to treat (NNT). Supporting materials, including detailed methods, tables and figures are available by contacting the authors (alexander.mcgirr@alumni.ubc.ca).

In total, we retained 19 RCTs in our meta-analysis[1-19], totaling 181 patients with bipolar disorder (type I, N=40; type II, N=20; unspecified, N=121). The RCTs employed different stimulation targets: the left dorsolateral prefrontal cortex (DLPFC)[1-6,9-11,13,16,17], the right DLPFC[8,14,15,18], or bilateral DLPFC[7,12,17,19]. The majority of studies delivered high-frequency stimulation (HFS)[1,3-6,9-13,16,18], while some delivered low-frequency stimulation (LFS)[3,8,9,15,18], sequential LFS and HFS[7,17,19], or theta burst stimulation (TBS)[2,14,17].

Significantly more patients receiving active rTMS achieved clinical response at study end compared to patients receiving sham rTMS (47/106, 44.3%, vs. 19/75, 25.3%; RD=0.18, 95% CI: 0.06-0.30, $p<0.01$). This represents a NNT of 6 (95% CI: 4-15). The fail-safe N was 29, suggesting that 29 missing or null studies are required to render this finding not statistically significant. Examination of the funnel plot revealed an asymmetrical distribution, with substantial loading at RD=0. Despite considerable methodological heterogeneity, there was no statistical evidence of heterogeneity ($Q=19.99$, $df=22$, $I2=0.00$, $p=0.58$; Egger's intercept =-0.36, $t(21)=0.42$, $p=0.67$).

The optimal stimulation target and parameters are important considerations in rTMS due to differing physiological effects. We observed a trend towards differential target efficacy ($Q=5.72$, $df=2$, $p=0.057$). Indeed, RCTs targeting the right DLPFC demonstrated superior efficacy, with 9/15 (60.0%) of active rTMS patients achieving clinical response compared to 1/15 (6.6%) of sham rTMS patients. This represents a RD of 0.48 (95% CI: 0.17-0.78, $p<0.001$) and a NNT of 3 (95% CI: 2-6). RCTs targeting the left DLPFC also separated from placebo, with 33/68 (48.5%) of patients receiving active rTMS achieving clinical response compared to 15/50 (30.0%) of sham-treated patients (RD=0.16, 95% CI: 0.00-0.31, $p<0.05$), for a NNT of 7 (95% CI: 4-112). We did not observe separation between active and sham rTMS in RCTs employing bilateral stimulation (5/23, 21.73% vs. 3/14, 21.42%, $p=0.68$). We did not observe differential efficacy based on stimulation parameters.

The issue of treatment-emergent affective switches in managing bipolar depression is important and controversial, and extends to neuromodulatory treatments. We observed a very low rate of treatment-emergent affective switches, and we did