Theta Burst Stimulation at 50Hz and 20Hz for TMS Treatment of Depression: A Case Series

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KEY MESSAGE

Theta Burst Stimulation (TBS) with either 50Hz (standard) or 20Hz (novel) pulse frequencies effectively treated depression in a real-world private practice setting. TBS 20Hz brought significantly more patients to remission than TBS 50Hz.

INTRODUCTION

- Standard clinical Transcranial Magnetic Stimulation (TMS) parameters, eg 10Hz Tonic, have remained largely unchanged for decades.
- Current TMS depression treatment is suboptimal, failing to bring the majority of patients to remission.
- TMS Theta Burst Stimulation (TBS), pulse triplets followed by a “rest” period, is a robust subthreshold pulse parameter with a short treatment session duration and indications of a longer lasting effect.
- TBS is rarely applied in clinical practice despite the potential benefits.
- Widespread clinical application of Theta Burst parameters could lead to improved treatment results.
- However, optimal theta burst frequencies for the treatment of depression have yet to be determined.

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OBJECTIVE

Report on the safety and efficacy of 50Hz and 20Hz Theta Burst TMS pulse parameters in patients with treatment-refractory depression.

Figure 1.
Theta Burst Pulse Diagram Explanation

10Hz Tonic Stimulation

Standard Theta Burst 50Hz

Novel Theta Burst 20Hz

Theta Burst Applied Continuously (Inhibitory)

Theta Burst Applied Intermittently (Excitatory)

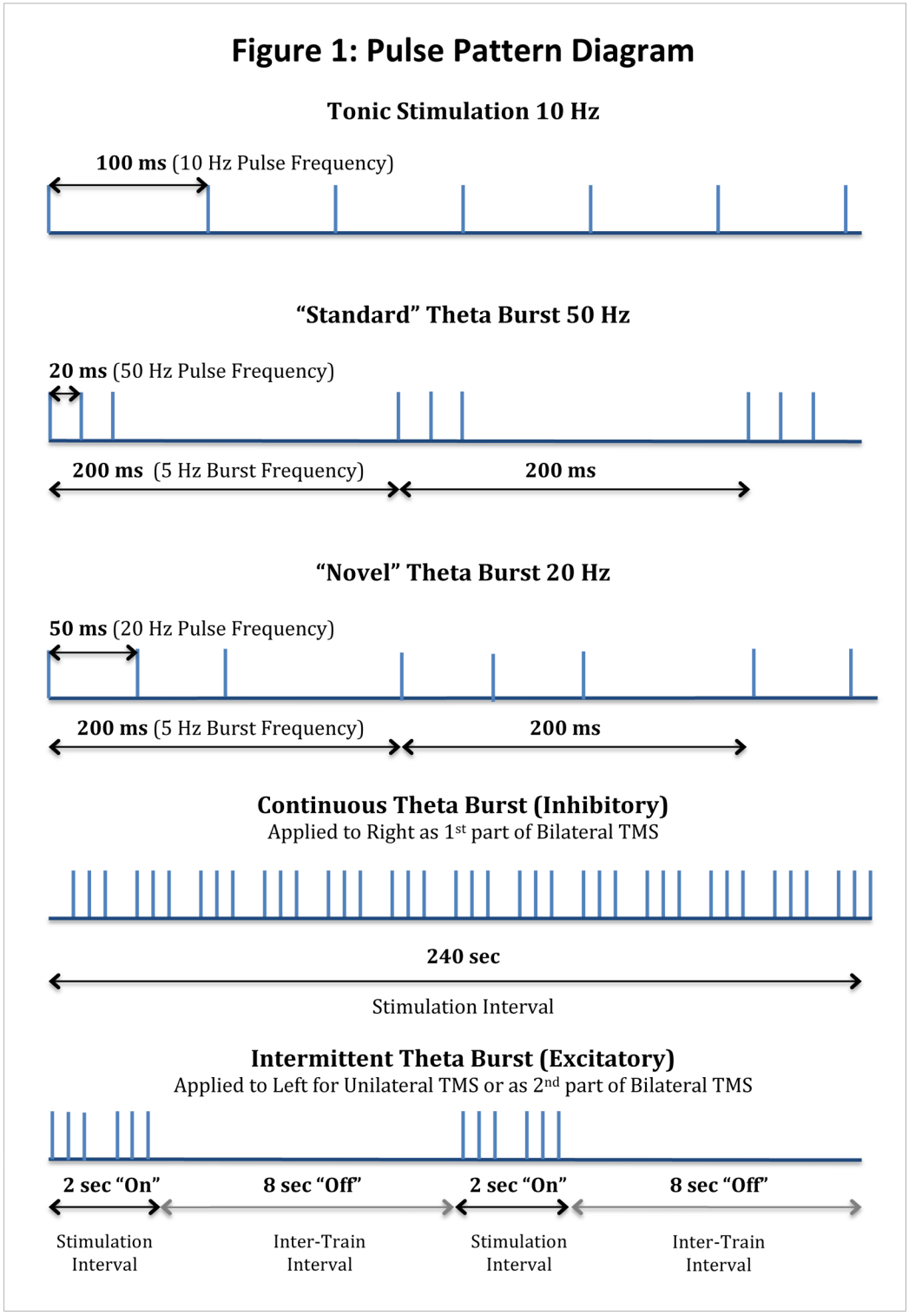

Table 1.
Patient Demographics

Table 1. Demographics/Clinical Characteristics

Patient	Age	Gender	Handedness	Diagnosis and Comorbid Diagnoses (DSM-IV)	Duration of Illness (Years)	Total Number of Failed Psychiatric Medications	Duration of Current Episode (Years)	Psychiatric Medications Taken Concurrently with Theta Burst Treatment*
1	62	M	Right	Major Depressive Disorder	7	10	7	Liothyronine Sodium. Lamotrigine, Melatonin, Nefazodone, Fluoxetine, Quetiapine, Zaleplon, Temazepam
2	23	M	Right	Major Depressive Disorder Social Phobia; Cocaine Dependence, in Remission; Opioid Dependence, in Remission	5	14	5	Aripiprazole, Zolpidem, Divalproex Sodium, Risperidone, Lisdexamfetamine Dimesylate
3	22	M	Right	Major Depressive Disorder, Generalized Anxiety Disorder; Polysubstance Abuse in Remission	10	8	4	Lamotrigine
4	64	M	Right	Major Depressive Disorder	30	9	30	Aripiprazole, Propranolol, Lamotrigine
5	83	M	Right	Major Depressive Disorder, Obsessive Compulsive Disorder	50	10	3	Zolpidem, Lamotrigine, Zaleplon, Sertraline
6	46	M	Right	Major Depressive Disorder	20	20	0.5	Sertraline, Bupropion Hydrochloride, Vortioxetine, Temazepam, Clonazepam
7	47	M	Right	Major Depressive Disorder, Obsessive Compulsive Disorder, Alcohol Dependence in Remission	8	4	5	Paroxetine, Ziprasidone, Divalproex Sodium, Gabapentin
8	56	F	Right	Major Depressive Disorder	24	6	6	Fluoxetine
9	83	F	Right	Major Depressive Disorder	38	40	38	Lorazepam, Paroxetine, Levothyroxine
10	36	M	Right	Major Depressive Disorder, Obsessive Compulsive Disorder, Alcohol Dependence in Remission	18	10	18	Escitalopram, Trazodone, Disulfiram, Lorazepam
MEAN:	**52.2**				**21.0**	**13.1**	**11.7**	
SD:	**21.7**				**14.8**	**10.4**	**12.8**	

*Patient 1 had a gap of seven months between Bilateral Theta Burst 50 Hz and Left Theta Burst 20 Hz phases of treatment due to the fact that Theta Burst 20 Hz was not available; patient 1 tapered off Lamictal and Prozac in the weeks leading to Theta Burst 20 Hz treatment, then restarted both at the same doses in the first two weeks of Theta Burst 20 Hz treatment. Seroquel was added for insomnia by his primary psychiatrist during Theta Burst 20 Hz treatment. Patient 4 tapered off Lamictal in the weeks leading to Theta Burst 50 Hz treatment, then restarted Lamictal in the first two weeks at the same dose.

Figure 2.
Theta Burst Treatment Sequence

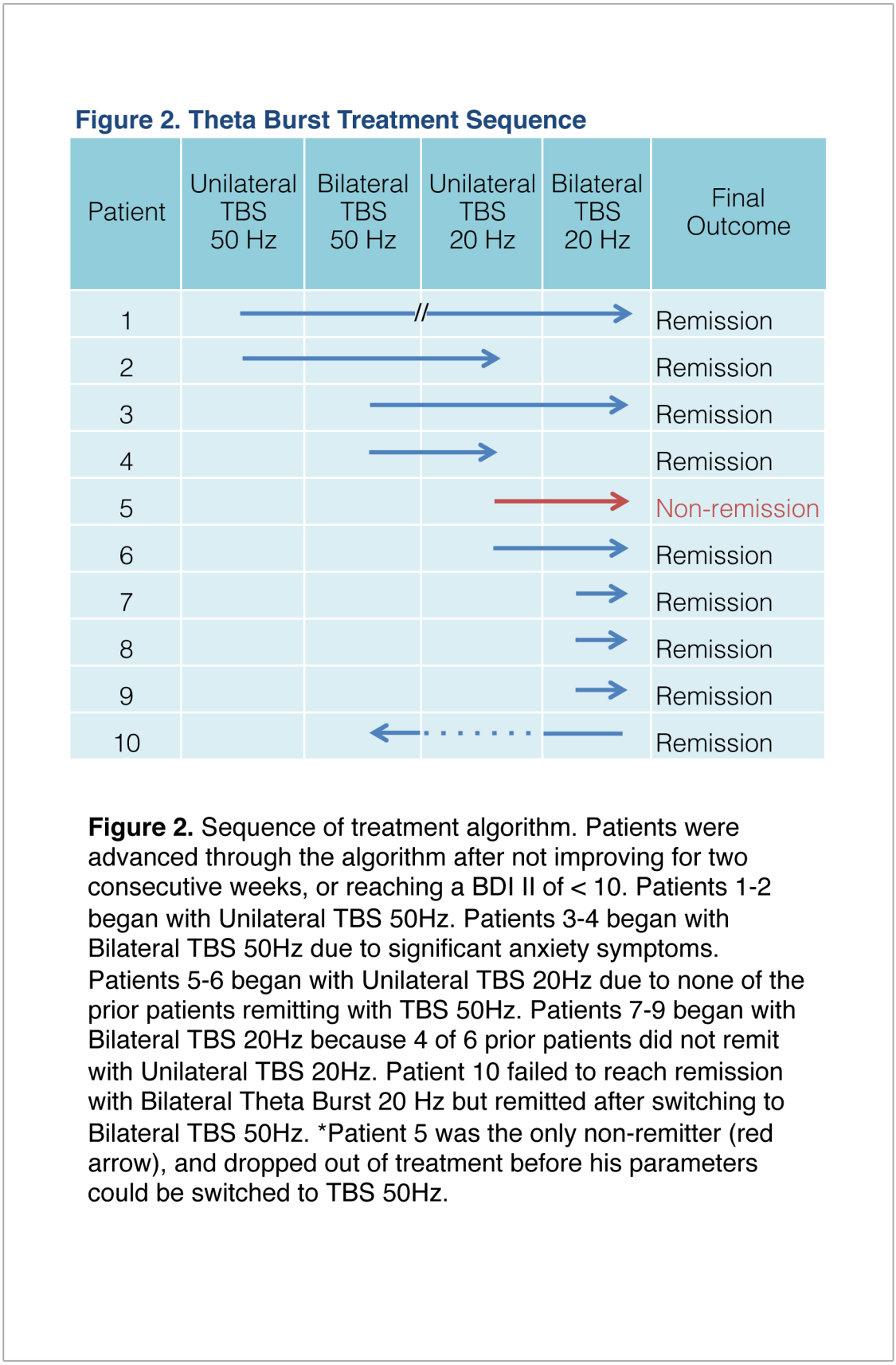

Figure 2. Sequence of treatment algorithm. Patients were advanced through the algorithm after not improving for two consecutive weeks, or reaching a BDI II of < 10. Patients 1-2 began with Unilateral TBS 50Hz. Patients 3-4 began with Bilateral TBS 50Hz due to significant anxiety symptoms. Patients 5-6 began with Unilateral TBS 20Hz due to none of the prior patients remitting with TBS 50Hz. Patients 7-9 began with Bilateral TBS 20Hz because 4 of 6 prior patients did not remit with Unilateral TBS 20Hz. Patient 10 failed to reach remission with Bilateral Theta Burst 20 Hz but remitted after switching to Bilateral TBS 50Hz. *Patient 5 was the only non-remitter (red arrow), and dropped out of treatment before his parameters could be switched to TBS 50Hz.

Figure 3.
Treatment Response for All Protocols

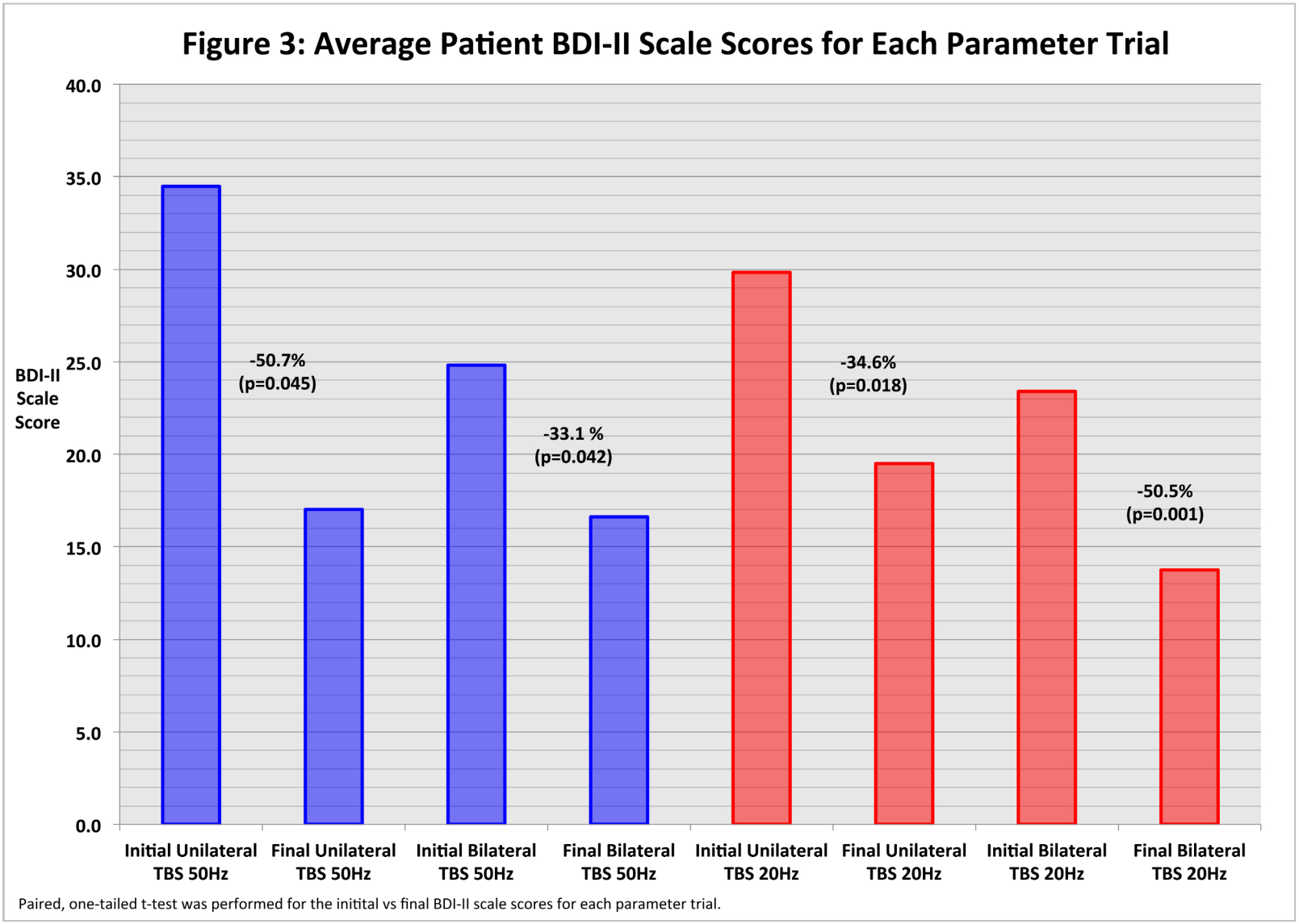

Figure 4.
Comparison of TBS 20Hz and TBS 50Hz Remission Rates

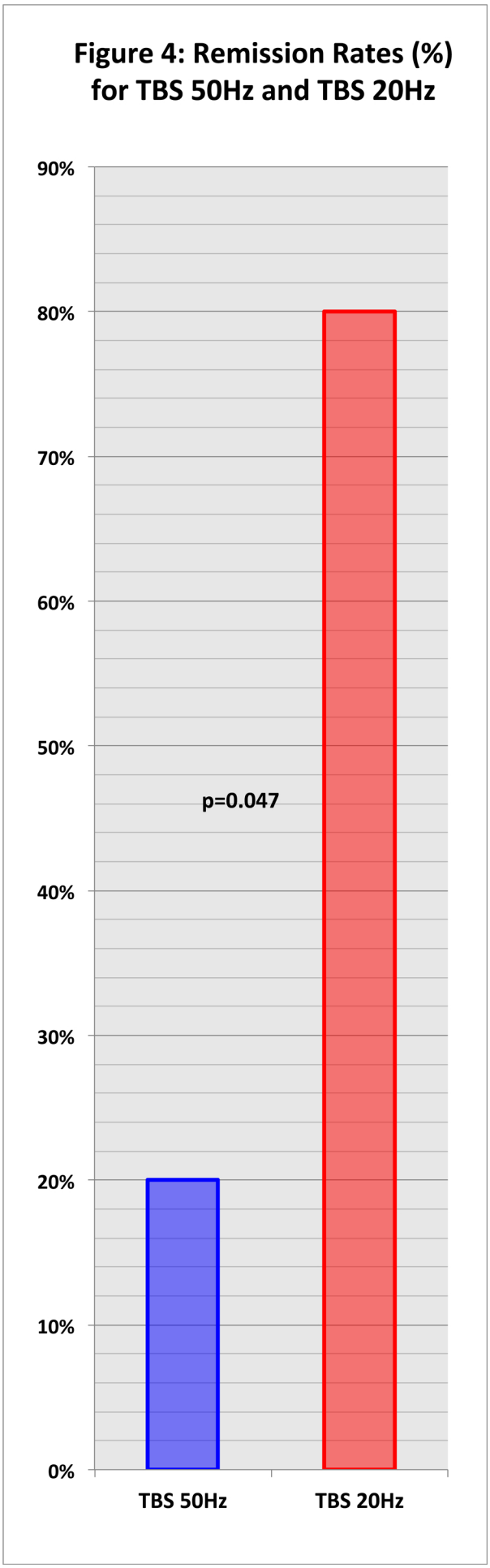

Table 2.
Protocol Parameters

Table 2: Protocol Parameters										
Protocol	Stimulation Site	Number of Pulses	Motor Threshold	Pulse Frequency (Hz)	Pulses/ Burst	Burst Frequncy (Hz)	Stimulation Interval (sec)	Intertrain Interval (Sec)	Emotionally Uplifting Music	Ear Plugs
Left Theta Burst 50 Hz	1. LDLPFC	4950	90%	50	3	5	2	8	x	
Bilateral Theta Burst 50 Hz	1. RDLPFC	3600	90%	50	3	5	239	0		x
	2. LDLPFC	4950	90%	50	3	5	2	8	x	
Left Theta Burst 20 Hz	1. LDLPFC	4950	90%	20	3	5	239	0	x	
Bilateral Theta Burst 20 Hz	1. RDLPFC	3600	90%	20	3	5	239	0		x
	2. LDLPFC	4950	90%	20	3	5	2	8	x	

Table 3.
Treatment Lengths

Table 3: Treatment Days Spent by Each Patient in Each Protocol							
Patient ID	Unilateral TBS 50Hz	Bilateral TBS 50Hz	Total TBS 50Hz	Unilateral TBS 20Hz	Bilateral TBS 20Hz	Total TBS 20Hz	Total TBS (50Hz and 20Hz)
Patient (Number)	Treatment Days	Treatment Days	Treatment Days	Treatment Days	Treatment Days	Treatment Days	Treatment Days
1	16	4	20	36	11	47	67
2	47	27	74	17		17	91
3		18	18	73	12	85	103
4		41	41	10		10	51
5				20	35	55	55
6				15	46	61	61
7					35	35	35
8					30	30	30
9					51	51	51
10		94	94		61	61	155
Mean	**31.5**	**36.8**	**49.4**	**28.5**	**35.1**	**45.2**	**69.9**
SD	**21.9**	**34.7**	**33.6**	**23.5**	**17.7**	**22.6**	**37.4**
ANOVA p value: 0.941							
Conclusion: Number of treatment days in each protocol is not significantly different.							

METHODS

- Ten treatment-refractory patients suffering from Major Depressive Disorder presented for treatment in a private practice setting (Table 1).
- Oral and written informed consent were obtained prior to treatment.
- TMS Equipment consisted of a MagPro X-100 with Mag Option and liquid-cooled B-65 figure-eight coil and ANT-Neuro Visor 2.0 Infrared Tracking Frameless Stereotaxy Neuronavigation System inputted with individual brain 3 Tesla MRI scans.
- Probabilistic centroid of Brodmann Area 46 was targeted with neuronavigation using Talairach coordinates.
- Patients were treated with a sequence of unilateral and/or bilateral TBS 50Hz and/or TBS 20Hz parameters as listed in Table 2 in the sequence described in Figure 2.
- Patients underwent an 8 week taper phase following remission (BDI-II<13).

RESULTS

- Nine of ten depression patients remitted with a combination of TBS 50Hz and TBS 20Hz.
- Eight of nine patients remitted with a final parameter of TBS 20Hz and one patient remitted with a final parameter of TBS 50Hz.
- BDI-II scale scores decreased significantly for all protocols (Figure 3). Average scale scores decreased for Unilateral and Bilateral TBS 50Hz by 50.7% (p=.045) and 33.1% (p=.042), respectively. Average scale scores decreased for Unilateral and Bilateral TBS 20Hz by 34.6% (p=.018) and 50.5% (p=.001), respectively.
- None of the first 4 patients who were started on TBS 50Hz remitted, while 4 of the subsequent 6 patients started on TBS 20Hz attained remission (p=.071, Fisher's exact).
- Six patients did not remit with the initial parameters. Five of six initial non-remitters switched parameter frequencies and eventually remitted, and one non-remitter dropped out of treatment before switching parameters. This resulted in 1 of 5 TBS 50Hz patients remitting and 8 of 10 TBS 20Hz patients remitting (p=.047, Fisher's exact). See Figure 4.
- Patients tolerated treatment well without adverse effects.

DISCUSSION

This case series evaluated only two possible theta burst parameters. The vast majority of potential parameter sets have yet to be explored. TMS remission rates could approach 100% if a greater variety of theta burst parameter frequencies were systematically tested and clinically applied.

CONCLUSION

Theta Burst 50Hz and 20Hz were safe and effective TMS treatment parameters for depression; however, TBS 20Hz brought more patients to remission than TBS 50Hz. Controlled trials are warranted.