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Rate of switch from bipolar depression into mania after morning light therapy: A historical review

Francesco Benedetti*

Psychiatry & Clinical Psychobiology, Scientific Institute Ospedale San Raffaele, Via Stamira d'Ancona 20, 20127 Milano, Italy

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ABSTRACT

Light therapy (LT) is efficacious for bipolar depression with effect sizes equivalent to those in antidepressant pharmacotherapy trials. Patients with bipolar disorder (BD) show a 15–40% rate of manic switches during antidepressant drug treatment. The rate of manic switches during LT has never been estimated.

We searched all the literature studies reporting effects of antidepressant LT in BD. 41 studies described 799 patients with BD treated with antidepressant LT, from among which 7 (0.9%) switched into mania and 11 (1.4%) switched into hypomania. The method of assessment of treatment-emergent symptoms significantly influenced the detection of switches into mania: 0% when no method was reported, 0.8% with clinical mental state examination, and 3% with rating scales (χ^2 = 14.805, d.f. 4, p = 0.005). The rate of switch increased to 18.8% when considering the 16 patients with rapid-cycling BD. Switches occurred independent of treatment modality (light intensity, duration, and circadian timing of administration).

The available literature shows that the highest reported rate of switch from bipolar depression into mania after LT is closely similar to the 4% switch rate expected during the placebo treatment of BD, thus not justifying specific concerns when using this treatment option.

Depression is the predominant abnormal mood state of patients with bipolar disorder (BD) (Kupka et al., 2007). It is a difficult-to-treat condition, with low success rates of antidepressant drugs in naturalistic settings (Post et al., 2011) and with the repeated use of antidepressant drugs being related to poor prospective response (Post et al., 2012). Prolonged and highly complex medication regimens are often needed to achieve a stable response in BD (Post et al., 2010). Hence the clinical usefulness of chronotherapeutic techniques, such as sleep deprivation (SD) and bright light therapy (LT), which can be used in everyday clinical practice (Benedetti et al., 2007a), to skip the latencies of traditional antidepressant treatments, and to target the core depressive symptoms of BD psychopathology (Benedetti et al., 2007b, 2014; Benedetti and Colombo, 2011).

The scientific approach to the treatment of depression with LT started in the '80 s, and since the very beginning LT was administered to patients with bipolar depression (Kripke, 1981; Kripke et al., 1983; Lewy et al., 1982; Rosenthal, 2000). Morning LT is efficacious for non-seasonal depression with effect sizes equivalent to those in most antidepressant pharmacotherapy trials (Golden et al., 2005), and it is synergistic and well tolerated when combined with antidepressant drugs (Benedetti et al., 2003; Lam et al., 2016; Martiny et al., 2005). A recent meta-analysis including nine studies with 489 patients with bipolar depression confirmed that disease severity was significantly decreased after LT (Tseng et al., 2016). Randomized controlled studies, also including crossover trials, associated best antidepressant responses to LT when given in the morning, in respect to LT given in the evening (Eastman et al., 1998; Lewy et al., 1998; Terman et al., 2001, 1998). However, the meta-analyses of randomized controlled trials limited their focus to efficacy, and cautioned that any potential recommendation of LT for mood disorders must be tempered by the acknowledgment that safety must also be considered (Golden et al., 2005).

Switching from depression into mania is a common occurrence in the lifetime history of patients with mood disorders. It is expected to occur in about 6–8% of patients with previously diagnosed unipolar major depressive disorder (MDD) who receive treatments with antidepressant drugs (Baldessarini et al., 2013; Tondo et al., 2010). The switch process is a fundamental and defining characteristic of BD (Goodwin and Jamison, 2007), and, based on available clinical trial data, the rate of switch into mania during treatment with placebo has been calculated at 4.2% for patients with BD (Peet, 1994). This rate raises to 15–40% when patients with BD are treated with antidepressant drugs (Goldberg and Truman, 2003; Niitsu et al., 2015; Post et al., 2006; Tondo et al., 2010). Powerful chronotherapeutic interventions aimed at the treatment of drug-resistant bipolar depression, such as

* Corresponding author.
E-mail address: benedetti.francesco@hsr.it.

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Table 1
Number of patients with BD treated with antidepressant LT. Methods for switch assessment: NR = Not reported; MSE = clinical mental state examination; YMRS = Young Mania Rating Scale; SADS = Schedule for Affective Disorders and Schizophrenia; HIGH-SAD = Hypomania Interview Guide for Seasonal Affective Disorder; BHGR = Bunney-Hamburg global ratings of depression and mania; SEQ = Light Visor Side Effect Questionnaire; SAFTEE = Systematic Assessment For Treatment Emergent Events; SCL-58 = Symptom Checklist-58 items; CPRS = Comprehensive Psychopathological Rating Scale; POMS-B = Profile of Mood States - Bipolar Form; SADS-MRS = mania rating items from the Schedule for Affective Disorders and Schizophrenia.

Authors	Treated patients	Switch assessment	Manic switches	Hypomanic switches	LT intensity (lux) x daily exposure (min)	Treatment duration (days)	Notes
(Lewy et al., 1982)	1	MSE	0	0	2000 × 360	10	LT given for 180 min in the morning, and 180 min in the evening
(Kripke et al., 1983)	3	MSE	0	0	1500 × 60	2	Intensity ranging from 1000 to 2000 lx
(Rosenthal et al., 1984)	27	MSE	0	0	2500 × 360	14	LT given for 180 min in the morning, and 180 min in the evening
(Rosenthal et al., 1985)	14	MSE	0	0	2500 × 360	7	LT given for 180 min in the morning, and 180 min in the evening
(Wehr et al., 1985)	4	BHGR	0	0	3000 × 480	1	LT given during a night of total SD
(Peter et al., 1986)	8	NR	0	0	1800 × 180	5	LT given for 90 min in the morning, and 90 min in the evening
(Yerevanian et al., 1986)	3	MSE	0	0	2000 × 120	7	LT given either in the morning or in the evening
(Heim, 1988)	50*	NR	0	0	2200 × 180	5	LT given for 90 min in the morning, and 90 min in the evening *Diagnosis was 'cyclothymic axis syndrome'
(Deltito et al., 1991)	6	HIGH-SAD	0	0	2500 × 120	7	–
(Oren et al., 1991)	4	NR	0	0	2500 × 120	14	LT given with red light for 7 days and with green light for 7 days
(Mackert et al., 1991)	3	NR	0	0	2500 × 120	7	–
(Kripke et al., 1992)	10	MSE	0	2**	2500 × 180	7	LT given in the evening **Author state that 'two subjects became mildly hypomanic', but do not specify their diagnosis (total sample size n = 25)
(Joffe et al., 1993; Levitt et al., 1993)	4	SEQ	0	0	3500 × 30	24	–
(Rosenthal et al., 1993)	1	SEQ	0	0	6000 × 60	7	–
(Bauer, 1993)	3	YMRS	0	0	2500 × 120	42	The sample also included 9 MDD patients, from among which 'four depressives developed clinically significant hypomanic symptoms during the treatment protocol, and would have met criteria for hypomania had symptoms endured for several days'
(Labbate et al., 1994)	3	SAFTEE	0	1	2500 × 120	14	LT given either in the morning or in the evening Author state that 'one patient experienced a single day of hypomanic symptoms that resolved with decreased light', but do not specify diagnosis (total sample size n = 30)
(Kusumi et al., 1995)	2	MSE	0	0	3000 × 120	21	Rapid-cycling BD
(Leibenluft et al., 1995)	13	MSE	0	2	10000 × 60	90	Rapid-cycling BD LT given either in the morning, at midday, or in the evening Author state that 2/5 patients given morning LT switched into hypomania, with subsequent worsening of their rapid-cycling. Not clear if LT was continued during hypomania.
(Papatheodorou and Kutcher, 1995)	7	SCL-58	0	0	10000 × 90–120	7	LT given for 45–60 min in the morning, and 45–60 min in the evening
(Thalen et al., 1995)	9	CPRS	0	0	1500 × 60	10	LT given either in the morning (n = 2) or in the evening (n = 7)
(Yamada et al., 1995)	7	NR	0	0	2500 × 120	7	–
(Terman et al., 1996)	18	NR	0	0	2500 × 120	7	–
(Terman et al., 1996)	18	NR	0	0	10000 × 30	14	LT given either in the morning or in the evening

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