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Antidepressant-associated maniform states in acute treatment of patients with bipolar-I depression

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Abstract Medical records of 158 patients with bipolar depression were analysed for the incidence of a switch from depression to maniform states (mania and hypomania). Relation to psychopharmacological treatment was investigated. Thirty-nine (25%) patients of the total sample had switched to a maniform state during the treatment period in the hospital. Among that group the phenomenon occurred in 23 patients (15%) as a hypomania and in 16 patients (10%) as a mania. Patients with a switch were significantly more often treated with tricyclic antidepressants (TCA) than patients without switch (79.5% vs 51.3%). Mood stabilising medication might reduce the risk for switching, especially in patients treated with TCA; however, it seems not totally sufficient, since 59% of the switched patients received mood stabilisers. The switch phenomenon was not associated with sociodemographic or clinical data.

Key words Bipolar-I depression · Switch · Antidepressants · Mood stabiliser

Introduction

Although efficacy of antidepressant drugs in acute treatment and relapse prevention of recurrent depression has been well documented in the years since their introduction, several questions remain unanswered. The use of antidepressants in treatment of bipolar depression is still a point of controversy. Clinical impression, case reports and results from different studies have suggested that antidepressant medication, especially tricyclic drugs, might adversely affect the course of illness in terms of inducing the rapid cycling phenomenon or a switch into maniform states (e.g. Akiskal 1980; Altshuler et al. 1995; Boerlin et al. 1998; Prien et al. 1984; Wehr et al. 1987). For example, Altshuler et al. (1995) concluded on the basis of a study on the longitudinal course of 51 patients with treatment-refractory bipolar disorder that the occurrence of manic episodes is likely to be antidepressant induced and not attributable to the expected course of illness in one third of the cohort. Switch rates of patients taking heterocyclic antidepressants have been reported to occur at approximately double the rate of that seen in patients taking non-heterocyclic antidepressant medication or placebo. Peet (1994) found that the rate of manic switch in bipolar patients treated with selective serotonin reuptake inhibitors (SSRIs) was no greater than that in the placebo-treated patients, but was substantially and significantly lower than the 11.2% rate of a manic switch in patients treated with tricyclic antidepressants (TCAs). He concluded, that patients who are perceived as being at risk for antidepressant-induced mania should be treated with SSRIs rather than TCAs. Evidence for the potency of antidepressants to induce a switch into mania comes also from the observation that antidepressant-induced manic episodes can also occur in patients suffering from psychiatric disorders, in which mania is not part of the natural course of illness (Berk et al. 1996; Vieta et al. 1992). Contradictory to these findings, Lewis and Winokur (1982) found, on the basis of a retrospective chart review, that a switch into mania occurred during 23% of admission when TCAs were used, and in 34% of admission when no treatment was given. They concluded that TCAs do not increase the risk for switching into mania, and that the so-called switch effect due to TCAs reported in the past probably represents random manifestations of bipolar illness. Angst's (1985) analysis of patterns of admissions to a Swiss psychiatric hospital (Burghölzli) from 1920 to 1982 goes in the same direction. He argued that after the introduction of antidepressants in 1958 there was no significant increase in switches of unipolar or bipolar patients, and that there was no evidence for treatment-induced switching.

In summary, the answer to the question as to whether the choice of an antidepressant, mood stabilising treat-

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ment or other factors affect the frequency or intensity of switching in bipolar depression remains unanswered. To further evaluate these questions, we analysed retrospectively medical records of bipolar-I depressed patients receiving naturalistic treatment to examine the incidence of switch phenomena and its relation to psychopharmacological treatment.

Subjects and methods

The aim of this study was to find out whether tricyclic antidepressants contribute to increasing the incidence of switching from depression to maniform states in patients with bipolar depression.

The study was based on a retrospective analysis of medical records of inpatients fulfilling the criteria mentioned herein. The inclusion criteria were:

1. Diagnosis of a bipolar affective disorder according to ICD-9 (ICD-9:296.3)
2. Hospitalisation in the Psychiatric hospital of the Ludwig-Maximilians University, Munich, between the years 1990 and 1997
3. No signs for organic brain disease
4. No alcohol or drug abuse

Medical records from these patients were analysed for the antidepressant treatment strategies and the occurrence of switching from depression to maniform states. Maniform states were divided into hypomania and mania according to the doctor's estimation in the medical records.

Drugs with a possible influence on the occurrence of switch phenomena were categorised according to medication classes: TCAs, monoamine oxidase inhibitors (MAOIs), SSRI, other antidepressants (tetracyclic drugs, newer antidepressants such as venlafaxine, nefazodone, etc.), mood stabilisers (lithium, carbamazepine and valproate) and neuroleptics. Any further medication was not taken into account for analysis of the data presented herein. Sociodemographic data were derived from the extensive documentation system of our hospital. The psychopathology was assessed in a standardised manner by using the AMDP system at time of admission and at discharge. The AMDP system is a comprehensive rating instrument that is based on traditional descriptive psychopathology and covers the whole psychopathological manifestations of functional psychoses. Each AMDP item can be considered on a four-point (0–3) scale. Principal component analysis of AMDP ratings lead to several syndromal dimensions (Pietzcker et al. 1983). For this study, the depressive syndrome (13 items, maximum score is 39), the manic syndrome (7 items, maximum score is 21) and the paranoid–hallucinatory syndrome (13 items, maximum score is 39) was calculated. Statistical analyses were carried out using the SPSS 7.5 Software for Windows (Microsoft, Seattle, Washington). Group differences for sociodemographic and clinical data were compared by using Student's *t*-test. Group differences for psychopharmacological treatment at the time of remission of the depressive symptomatology were compared by using the chi-square test. A *p*-value of 0.05 (two-tailed) was considered as statistically significant.

Results

Switch rate, sociodemographic and clinical characteristics

Thirty-nine patients (25%) from a total of 158 patients switched to a maniform state during the treatment period in the hospital. Among that group the phenomenon manifested in 23 patients (15%) as a hypomanic and in 16 patients (10%) as a manic state.

A correlation of the switch phenomenon with sociodemographic or clinical characteristics of patients could not be detected (Table 1). The affective psychopathology (manic and depressive syndrome) was equally expressed in both groups at the time of admission. The same was true for the paranoid–hallucinatory syndrome (Table 1).

Switch rate and psychopharmacological treatment

A first exploratory analysis of psychopharmacological treatment (Table 2) indicates that patients with a switch phenomenon were significantly more frequently treated with tricyclic antidepressant drugs than patients without switch. Significant differences for treatment frequency with other antidepressant drugs (SSRI, MAOI, etc.) were not found. Neuroleptics, which may prevent a switch to a maniform state, were equally prescribed in the switch and non-switch group, too. Switch rates were 33.7% for the TCAs, 12% for the SSRI, 8.33% for the MAOI and 13.6% for the other antidepressants.

Results concerning a mood-stabilising comedication are as follows: no significant differences were found for the single substances of mood stabilisers between both outcome groups. However, according to global categorisation (i.e. patient receives any of the following mood stabilisers: carbamazepine, lithium, valproic acid or combinations), group differences were significant: 59% of pa-

Table 1 Comparison of sociodemographic and clinical data for the switch and non-switch group

	Switch group	Non-switch group	*p* value
No. of patients	39	119	
Gender (female/male)	27/12	81/38	n.s.
Age (years, mean ± SD)	54.79 ± 14.45	51.88 ± 15.14	n.s.
Duration of illness (years)	19.23 ± 14.45	17.4 ± 12.64	n.s.
No. of prior episodes of mania	4.87 ± 7.09	3.39 ± 3.87	n.s.
No. of prior episodes of depression	7.64 ± 7.13	6.85 ± 8.12	n.s.
Manic syndrome (mean ± SD)	0.9 ± 1.43	0.76 ± 1.43	n.s.
Depressive syndrome (mean ± SD)	16.56 ± 7.66	15.83 ± 7.36	n.s.
Paranoid-hallucinatory syndrome (mean ± SD)	0.26 ± 0.79	0.40 ± 1.29	n.s.
Duration of stay in hospital (days)	63.26 ± 27.13	58.43 ± 35.55	n.s.

Table 2 Comparison of psychopharmacological treatment not distinguishing between antidepressant monotherapy and combinations of antidepressants and mood stabilisers (*TCA* tricyclic antidepressants; *MAOI* monoamine oxidase inhibitors; *SSRI* selective serotonin reuptake inhibitors)

	Switch group [*n* (%)]	Non-switch group [*n* (%)]	*p* value
Antidepressants			
TCA	31 (79.5)	61 (51.3)	0.002
MAOI	1 (2.6)	11 (9.2)	n.s.
SSRI	3 (7.7)	22 (18.5)	n.s.
Other	3 (7.7)	19 (16)	n.s.
Overall (antidepressants)	38 (97.4)	113 (95)	n.s.
No antidepressant	1 (2.6)	6 (5)	n.s.
Neuroleptics	19 (48.7)	48 (40.4)	n.s.
Mood stabilisers			
Lithium	16 (41)	64 (53.8)	n.s.
Carbamazepine	2 (5.1)	16 (13.4)	n.s.
Valproate	0 (0)	1 (0.8)	n.s.
Combinations	5 (12.8)	17 (14.3)	n.s.
Overall (mood stabilisers)	23 (59.0)	98 (82.4)	0.003

Table 3 Comparison of psychopharmacological treatment analysing the impact of mood stabilisers

	Switch group [*n* (%)]	Non-switch group [*n* (%)]	*p* value
Antidepressant without mood stabiliser			
TCA	13 (33.3)	10 (8.4)	< 0.001
MAOI	0 (0)	2 (1.7)	n.s.
SSRI	2 (5.1)	6 (5.0)	n.s.
Other	1 (2.6)	1 (0.8)	n.s.
No antidepressant	0 (0)	2 (1.7)	n.s.
Overall (without mood stabiliser)	16 (41)	21 (17.6)	0.003
Antidepressant with mood stabiliser			
TCA	18 (46.2)	51 (42.9)	n.s.
MAOI	1 (2.6)	9 (7.6)	n.s.
SSRI	1 (2.6)	16 (13.4)	n.s.
Other	2 (5.1)	18 (15.1)	n.s.
No antidepressant	1 (2.6)	4 (3.4)	n.s.
Overall (with mood stabiliser)	23 (59)	98 (82.4)	0.003

tients with a switch, but 82.4% of patients without a switch, took mood stabilisers. A more detailed analysis for patients taking antidepressants with or without mood-stabilisers is presented in Table 3. The frequency of taking antidepressants without a mood-stabilising medication was compared between both outcome groups. This comparison was only significant for the TCAs, showing a higher rate in the switch group than in the non-switch group. The frequencies for taking combinations of antidepressants and mood stabilisers were not significantly different for the switch and non-switch groups. The switch rate was significantly reduced when TCAs were combined with mood stabilisers in comparison with the switch rate during treatment with TCAs without mood stabiliser [18 of 69 (26.1%) vs 13 of 23 (56.5%), chi-square = 0.007]. Such a decrease in switch rates was found to be not significant for SSRI, MAOI and the other antidepressants.

Discussion

Despite some limitations of our study, because of its naturalistic and retrospective character, our data give further support to previous observations that especially therapy with classical tricyclic drugs increases the risk for switching to a maniform state. The overall switch rate was 25% in 158 patients with bipolar-I depression. Of the switched patients, 79.5% received a tricyclic antidepressant, whereas this percentage was significantly lower in the non-switch group (51.3%). Significant differences in the frequency of use of the other antidepressant drugs in both outcome groups were not detected. Overall switch rates were 33.7% for the TCAs, 12% for the SSRI, 8.33% for the MAOI and 13.6% for the other antidepressants. Comparable findings are reported by Peet (1994) who found a significantly higher switch rate for treatment with TCA (11.2%) compared with patients taking paroxetine or sertraline (3.7%).

Himmelhoch et al. (1991) observed a switch rate of 38% for bipolar-I patients treated over a 16-week period with antidepressants. Concomitant mood stabilisers were not allowed in this study. Boerlin et al. (1998) found in a study on 29 bipolar-I patients that switches to hypomania or mania occurred in 28% of the overall number of episodes. The switch rate for antidepressant-treated index episodes was 15%. Depressive episodes treated with TCAs or MAOIs were more frequently marked by switching than those treated with fluoxetine, with TCA-induced switches being most intense, although these findings did not reach statistical significance.

Rouillon et al. (1992) provided an overview of 15 placebo-controlled studies. In patients specifically diagnosed as bipolar (n = 158), the incidence of maniform states was 51% in 49 patients treated with imipramine alone, 21% in 60 patients treated with lithium alone, 28% in 36 patients treated with lithium and imipramine, and 23% in 13 patients receiving only placebo. Altshuler et al. (1995) found in 51 patients with bipolar depression (38 bipolar I, 13 bipolar II) a switch rate of 82%; however, in only 35% of patients the manic episodes could be attributed to the antidepressants. Similar to our study, no demographic factors or illness variables were able to predict a patient profile with higher vulnerability to the antidepressant-induced switch phenomenon. Quitkin et al. (1981) found a rate of relapse into mania of 24% for bipolar-I depressed patients treated with lithium and imipramine, compared with a relapse rate of 10.5% for those taking lithium and placebo. Although the difference was not significant, it was suggestive of a correlation of imipramine treatment with an increased rate of switching from depression to mania. Additionally, results from Quitkin et al. (1981) can also be interpreted as an argument supporting the protective function of lithium. In our sample 59% of the switched patients had received a mood-stabilising medication (according to the global categorisation for getting any mood stabiliser). This percentage was significantly higher (82.4 vs 59%) in the non-switch group than in the switch group. The switch rate for treatment with TCAs was significantly reduced when TCAs were combined with mood stabilisers. The protective function of mood stabilisers is also supported by Prien et al. (1984) who found in a double-blind, long-term follow-up study the incidence of mania to be 53% for bipolar patients taking imipramine alone and only 26% for those taking lithium, and 28% for those taking lithium and imipramine. Differences among treatment groups were statistically significant; thus, these results support the protective function of lithium as well as the potency of imipramine to induce manic switches. In a study by Jann et al. (1982), 12 of 30 bipolar-depressed patients experienced a switch while treated with lithium. Patients with a switch were characterised by significantly lower lithium serum levels compared with non-switching patients. Boerlin et al. (1998) concluded on the basis of their results that mood stabilisers may reduce the risk for switching. These results were derived from a within-subject analysis, which verified the similarity in switch rates between patients who got mood stabilisers and those who got mood stabilisers plus an antidepressant.

In conclusion, our results are in line with the assumption that patients with bipolar-I depression are at a higher risk to switch into maniform states during treatment with TCAs. This increased risk may be reduced when antidepressants are combined with a mood-stabilising medication. Despite this evidence, it seems noteworthy that our results and results from others do not explain, for example, why some patients switch and others with the same medication do not. It seems clear that additional factors, e.g. sociodemographic, clinical and biological parameters, influence the switch process; however, the empirical data basis is rare and even contradictory. Aside from the limitations, our results may serve as a rationale for prospective investigations, which may provide more conclusive findings.

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