

A review of the evidence for carbamazepine and oxcarbazepine in the treatment of bipolar disorder

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Abstract

Bipolar disorder is a recurrent lifelong condition associated with significant morbidity and mortality. The main goals of treatment are the acute management of manic/depressive episodes and the prevention of recurrence. Mood stabilizers are the basis of most treatment regimens. Although lithium is the classical mood stabilizer, dissatisfaction with its efficacy and tolerability has led to increased use of other mood-stabilizing agents, including anticonvulsants. Newer anticonvulsants such as oxcarbazepine may offer improved tolerability and fewer drug–drug interactions compared to older drugs like carbamazepine. A search of the literature shows that data from controlled clinical studies support the efficacy of carbamazepine in treating acute mania and as maintenance therapy. In addition, a growing body of data for oxcarbazepine suggests that this newer agent may have a similar efficacy profile to carbamazepine, with improved tolerability. This review presents a balanced selection of the key studies on carbamazepine and oxcarbazepine in bipolar disorder.

Received 19 November 2003; Reviewed 18 February 2004; Revised 19 May 2004; Accepted 30 May 2004

Key words: acute mania, bipolar disorder, carbamazepine, mood stabilizer, oxcarbazepine.

Introduction

In comparison with other psychiatric conditions, bipolar disorder has been a relatively neglected disease, and thus the number of published clinical articles represents only a tenth of that available for schizophrenia and depression (Goodwin, 2000).

Nevertheless, approaches to the treatment of bipolar disorder have changed greatly in recent years. One of the main shifts in clinical practice has been away from the total acceptance of lithium as the first-line ‘wonder drug’ in mood stabilization and towards increasing the use of anticonvulsants as first-line and alternative agents. Anticonvulsants are a heterogeneous group of medications with a broad spectrum of efficacy in bipolar disorder (Hirschfeld et al., 2002).

In this review, we briefly consider the factors making bipolar disorder such an important and difficult condition to treat. Issues that have arisen with the

use of treatments such as lithium highlighted the need for alternative agents to treat patients with bipolar disorder. Consequently, this led to the use of anticonvulsants and antipsychotics as alternative therapies.

This review will focus on the available data for the efficacy of carbamazepine in the treatment of bipolar disorder. We then go on to present the data for the related compound, oxcarbazepine, a new generation anticonvulsant in the treatment of bipolar disorder.

Background

Disease burden

Bipolar disorder is a recurrent lifelong condition associated with significant morbidity and mortality. Disease onset is usually between ages 15 and 24 yr, although there may be a delay of many years before treatment is sought (Hirschfeld et al., 2002). Survival analysis has indicated that even with maintenance therapy, the 5-year risk of a further episode (manic or depressive) is 73% (Gitlin et al., 1995). Significant disability often results, and over the past decade bipolar disorder has ranked as high as sixth in the leading

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causes of disability worldwide (Murray and Lopez, 1996). Compared with the general population, patients with bipolar disorder are twice as likely to get divorced (Coryell et al., 1993), and twice as many have limited employment (Zwerling et al., 2002). At least 25% of bipolar patients attempt suicide and around 10–15% complete their attempt (Murray and Lopez, 1996).

Substance abuse is a common problem in bipolar disorder (present in approx. 50% of patients) and can both worsen the course of the condition and complicate treatment (Cassidy et al., 2001). Comorbid psychiatric and neurological disorders are also prevalent and include panic disorder, social phobia, obsessive-compulsive disorder and post-traumatic stress disorder (Freeman et al., 2002). It is not surprising then, that in 1991 the total costs to society for bipolar disorder in the USA were estimated at \$45 billion, approx. 70% of that for schizophrenia (Wyatt and Henter, 1995). In the UK, the total annual cost to society has been estimated at £2 billion, and it is significant that only 10% of this was attributed to health service resource use, while 86% was due to indirect costs (Das Gupta and Guest, 2002).

Diagnostic features

Although DSM-IV (APA, 1994) offers guidance on classifying bipolar disorders, current opinion acknowledges that this is a heterogeneous group of conditions ranging from a pattern of mild depression and brief hypomania to one of severe rapid cycling or mania with psychotic features. Notably, patients may present with a variety of clinical states (e.g. mania, hypomania, depression, mixed states) that overlap with other psychiatric illnesses. In terms of disease management, this means that the patient population is highly segmented, making differential diagnosis and treatment a difficult process. Consequently, the development of diagnostic subclassifications to assist with symptom-specific selection of treatment options is currently a major issue in bipolar disorder research (Müller-Oerlinghausen et al., 2002). Approx. 30% of depressed patients in the outpatient or family practice settings may have a bipolar spectrum illness (Sloan Manning et al., 1998). Sloan Manning and colleagues have suggested that a further classification of 'affective temperaments' is warranted (e.g. hyperthymic, dysthymic, and cyclothymic). These are patients whose symptoms of mania and depression are not severe enough to be classified as a formal mood disorder, but still disrupt functioning.

Current therapy

The main goals of treatment in bipolar disorder are the acute management of manic and depressive episodes and the prevention of future episodes. Mood stabilizers are currently the basis of most treatment regimens. Lithium is the classical mood stabilizer (its action was first noted by Cade in 1949), and there is good evidence suggesting that it prevents relapse and recurrence long term. In addition, patients with bipolar disorder who were receiving lithium had a lower risk of suicide attempt and suicide death than patients treated with divalproex, the most commonly prescribed mood-stabilizing drug in the USA (Goodwin et al., 2003).

However, clinicians have increasingly recognized that lithium may not be as effective as initial studies suggested. Although response rates of 80% are often cited, the largest controlled study of lithium in acute mania demonstrated only a 50% improvement after 3 wk in approx. 50% of patients (Bowden et al., 1994). Furthermore, many studies have suggested that a similar proportion of patients may have an inadequate prophylactic response to lithium, the most recent being Denicoff et al. (1994) and Gitlin et al. (1995). In addition, the side-effect profile of lithium makes compliance a significant problem.

These issues have prompted the investigation of other agents, the result of which has been the emergence of anticonvulsants, such as carbamazepine, valproate, and atypical antipsychotics (Kasper et al., 2002) as major mood-stabilizing alternatives to lithium. The majority of data in the public arena for anticonvulsants are for older compounds such as carbamazepine and divalproex although newer agents, such as oxcarbazepine, offer potential additional benefits such as improved tolerability and fewer drug–drug interactions. However, these newer agents have been studied less extensively.

This report will review the data for carbamazepine in bipolar disorder and highlight those studies that suggest potential efficacy of oxcarbazepine in these patient groups.

Search strategy

A computer-aided search of MEDLINE for the years 1966–2002 was conducted with the terms 'carbamazepine' or 'oxcarbazepine' in conjunction with other selected terms, including 'bipolar', 'mania', and 'manic'. Further information was obtained by searching the bibliographies of reference material obtained from the MEDLINE searches and by hand-searching

additional material. All material was reviewed, and key information is described in this article.

Carbamazepine

Carbamazepine is a widely used anticonvulsant that was first evaluated as a potential treatment in manic depressive psychosis by Takezaki and Hanaoka (1971), and Okuma et al. (1973). In 1979, Okuma et al. performed the first double-blind trial of carbamazepine in comparison with the antipsychotic chlorpromazine in mania and found that 70% and 60% of patients improved respectively. A further placebo-controlled double-blind study replicated the antimanic properties of carbamazepine under controlled circumstances (Ballenger and Post, 1980). There have since been many studies demonstrating the efficacy of carbamazepine in treating the acute manic and depressive symptoms of bipolar disorder, as well as in prophylaxis (Brambilla et al., 2001; De Léon, 2001; Post et al., 1996a).

Acute mania

Evidence from over 17 controlled studies supports the efficacy of carbamazepine in acute mania (Table 1). However, many of these studies are not robust by modern standards, as concomitant lithium and antipsychotics were permitted. Overall, five controlled studies did not permit concomitant medications of this kind (188 patients in total, Table 1). By switching patients from carbamazepine to placebo and back to carbamazepine, one study demonstrated a significant antimanic effect for carbamazepine (Ballenger and Post, 1980). Grossi et al. (1984) examined whether raising the relatively low doses (by Western standards) of carbamazepine and chlorpromazine would further confirm the antimanic effect of carbamazepine found by Okuma et al. (1979). In both studies, around 10% more patients receiving carbamazepine showed a moderate to marked response compared to chlorpromazine (Table 1). Lerer et al. (1987) found no significant difference in antimanic effect between carbamazepine and lithium over 4 wk (although carbamazepine exerted a lesser effect), and Small et al. (1991) observed similar improvements over 8 wk.

Considering all studies in mania, including those with weaker designs, carbamazepine has demonstrated a similar antimanic effect to antipsychotics and lithium. Double-blind comparisons (ranging from 3 to 5 wk duration) with chlorpromazine (300–900 mg/d carbamazepine vs. 150–450 mg/d chlorpromazine) (Okuma et al., 1979) or haloperidol (600–1200 mg/d

carbamazepine vs. 5–30 mg/d haloperidol) (Stoll et al., 1986) have shown similar efficacy, with a slightly slower onset of action for carbamazepine (400–1600 mg/d carbamazepine vs. 20–80 mg/d haloperidol) (Brown et al., 1989). In these studies, haloperidol and chlorpromazine were associated with a high rate of adverse events. Overall, the efficacy of carbamazepine and lithium in acute mania seen in double-blind studies is consistently similar (Lusznat et al., 1988; Okuma et al., 1990; Small et al., 1991) (Figure 1), with doses ranging from 200 to 1200 mg/d carbamazepine and from 400 to 1200 mg/d for lithium over 4–8 wk.

The efficacy of carbamazepine for treating bipolar disorder in children and adolescents (mean age 11.4 yr) has been suggested in a recent prospective, open study conducted in an outpatient setting. Carbamazepine (titrated to 7–10 µg/l) was compared with lithium (titrated to 0.8–1.2 mequiv./l) and divalproex sodium (85–110 µg/l) in 42 patients with mixed or manic episodes (Kowatch et al., 2000). Both carbamazepine and lithium showed a response rate of 38% on the Young Mania Rating Scale (YMRS), which the authors considered to be a large effect size. Divalproex sodium showed a response rate of 53%; however, some children receiving divalproex sodium experienced a transient worsening of symptoms after 3 wk treatment (Kowatch et al., 2000).

Furthermore, several double-blind comparative studies have shown the efficacy of carbamazepine in patients refractory to lithium (Lerer et al., 1987; Okuma et al., 1990; Post et al., 1987), suggesting that carbamazepine monotherapy may be best suited to this group.

Acute depression

Like most mood stabilizers, carbamazepine has been less intensively studied in the treatment of acute depression, although like lithium, it has been suggested that carbamazepine has a greater antidepressant effect in bipolar compared with unipolar depressive disorders (Ballenger, 1988). In keeping with this, a group of five small controlled studies suggest an overall (moderate-marked) response [defined as a decrease on the Bunney–Hamburg scale or the Hamilton Rating Scale for Depression (HRSD)] rate of 59% (51/86 patients) (Ballenger and Post, 1980; Neumann et al., 1984; Post et al., 1986; Rybakowski et al., 1999; Sethi and Tiwari, 1984). However, these studies mixed patients with bipolar and unipolar depression and results were not always consistent. Two open studies found that 55% of patients with major depression

Table 1. Controlled studies of carbamazepine in acute mania

Study	Design	Duration	Treatment (daily dose, mg)	Patients [mean age (range), yr]	Outcome measures	Responders
Concomitant mood stabilizers not permitted						
Okuma et al. (1979)	r, db	3 wk	CBZ (300–900) vs. CPZ (150–450)	60 bipolar and unipolar manic [36 (16–70)]	CPRG	21 (70%) CBZ, 15 (60%) CPZ
Ballenger and Post (1980)	db, pc	6 wk	CBZ (600–2000)/placebo/CBZ	9 bipolar [39 (23–61)]	Bunney–Hamburg, BPRS	12 (56%) CBZ, 3 (60%) placebo
Grossi et al. (1984)	r, db	3 wk	CBZ (200–1200) vs. CPZ (200–800)	37 bipolar (46 ± 15)	MSRS, BMS	10 (67%) CBZ, 13 (59%) CPZ
Lerer et al. (1987)	r, db	4 wk	CBZ (600–2600) vs. Li (900–3900)	34 bipolar [40 (23–65)]	CGI, BPRS, MSRS	4 (27%) CBZ, 1 (58%) Li
Small et al. (1991)	r, db	8 wk	CBZ (700–1036) vs. Li (1035–1278)	48 bipolar [39 (22–73)]	SDMS-D&M, YMS, BPRS, CGI	8 (33%) CBZ, 8 (33%) Li
Concomitant mood stabilizers permitted						
Klein et al. (1984)	r, db, pc	5 wk	CBZ (600–1200) + HAL (15–45) vs. CBZ (600–1200) + placebo	22 bipolar, 11 schizoaffective, 10 schizophrenic [34 (20–70)]	BPRS, CGI	Improvement 18% greater in the CBZ + HAL group compared to the CBZ + placebo group
Sethi and Tiwari (1984)	r	4 wk	CBZ (600–1600) vs. CPZ (600–1300)	10 bipolar [36 (18–50)]	BRMRS, CGI	No significant difference between CBZ and CPZ after 4 wk, but there was a tendency in favour of CBZ 100% patients improved by CGI for CBZ and CPZ
Goncalves and Stoll (1985)	r, db, pc	3 wk	CBZ (200–1200) vs. placebo	7 bipolar, 5 schizoaffective [43 (22–65)]	MS-M	6/6 patients with greater improvement than placebo ($p < 0.01$)
Stoll et al. (1986)	r	3 wk	CBZ (600–1200) vs. HAL (5–30)	34 manic, 24 schizoaffective (40 ± 13.4)	MS-M	12/16 (75%) improved ('good' to 'very good') on CBZ, 12/18 (67%) improved on HAL, $p < 0.05$
Lenzi et al. (1986)	r, db	3 wk	CBZ (400–1600) + CPZ (n/a) vs. CBZ (400–1600) + Li (300–900)	22 bipolar, 3 schizoaffective, 5 other (39 ± 14)	BPRS, CGI	Significant improvement on CGI and BPRS with CBZ + Li
Desai et al. (1987)	r, db, pc	4 wk	CBZ (400, fixed dose) vs. placebo addition to Li	10 manic (na)	BRMRS, GMS	CBZ + Li produced significantly greater improvements on the BRMRS and GMS than Li alone
Okuma et al. (1988)	db, pc	Variable	CBZ (n/a) vs. placebo	201 manic (na)	Global assessment	50% improvement (moderate to marked) with CBZ, 30% with placebo
Moller et al. (1989)	r, db, pc	3 wk	CBZ (600) + HAL (24) vs. CBZ (600) + placebo	12 manic, 8 schizomanic (33 ± 13)	BRMRS, BPRS, MS-M	Significant antimanic effect on all scales for both treatment groups

Okuma et al. (1990)	r, db	4 wk	CBZ (400–1200) vs. Li (400–1200)	101 manic [36 (19–70)]	CPRG	No significant difference between groups 31/50 (62%) improved on CBZ 30/50 (59%) improved on Li CBZ had a faster onset of action Similar improvements of >50% in both groups
Small et al. (1995)	r, db	8 wk	CBZ (≥ 500 – ≥ 900) + Li (900–1400) vs. Li (900–1400) + HAL (11.0–13.5)	33 bipolar [37 (19–62)]	MSRS	
Vasudev et al. (2000)	r	4 wk	CBZ vs. VPA	30 bipolar (na)	Global assessment	53% CBZ, 73% VPA

Abbreviations: r, randomized; db, double blind; pc, placebo controlled; CBZ, carbamazepine; CPZ, chlorpromazine; Li, lithium; VPA, valproate; CPRG, Clinical Psychopharmacology Research Group Scale for mania; Bunney–Hamburg, Bunney–Hamburg Rating Scale; BPRS, Brief Psychiatric Rating Scale; MSRS, Manic State Rating Scale; BMS, Bipolar Mania Scale; SDMS-D&M, manic subsection of the Depression and Mania Scale; YMS, Young Mania Scale; CGI, Clinical Global Impression Scale; MS-M, Murphy Scale for Mania; GMS, Global Mania Scale.

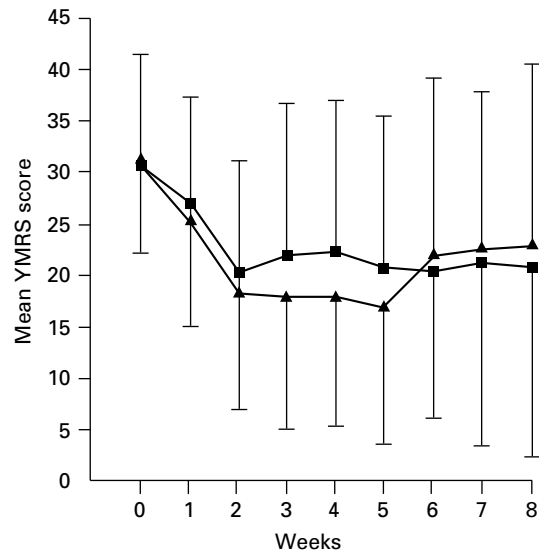


Figure 1. Similarity of antimanic effect with lithium (■) and carbamazepine (▲) (adapted from Small et al., 1991, with permission). YMRS, Young Mania Rating Scale.

or bipolar disorder had an improvement following treatment with carbamazepine (Wunderlich et al., 1982a,b), and therapy-resistant patients were also found to exhibit a response to carbamazepine (Emrich et al., 1985; Prasad, 1985). In addition, three other studies have found that carbamazepine is associated with efficacy in treating patients with depression (Kravitz and Fawcett, 1987; Post et al., 1986; Strömgen and Boller, 1985). Consequently, it is recommended that patients already receiving carbamazepine prophylaxis should continue to do so, but the use of carbamazepine monotherapy for the prevention of depressive episodes is not strongly supported with the existing data (Grunze et al., 2002).

Two of these five controlled studies followed a double-blind, off-on-off design lasting 6–8 wk and demonstrated that at doses of 200–2200 mg/d, the acute antidepressant effect of carbamazepine was superior to placebo (Ballenger and Post, 1980; Post et al., 1986). A total of 5 out of 13 (38%) and 20 out of 35 (57%) carbamazepine patients (including bipolar and unipolar depressed) were classed as responders on the Bunney–Hamburg Rating Scale. In addition, three randomized 4-week studies have shown that carbamazepine (400–1800 mg/d) is not significantly different from either trimipramine (150–800 mg/d) or imipramine (75–200 mg/d) when administered as monotherapy (Neumann et al., 1984; Sethi and Tiwari, 1984), or to lithium (500–1500 mg/d) when used to augment antidepressant therapy (Rybakowski et al., 1999). During 28 d treatment, carbamazepine showed

a marked antidepressant effect and a faster onset of action than trimipramine and imipramine, and patient self-rating scales were also more favourable for carbamazepine (Neumann et al., 1984; Sethi and Tiwari, 1984). As combination therapy with an antidepressant, 28 d treatment resulted in 57.1% and 67.7% of patients being classed as responders for carbamazepine and lithium respectively (Rybakowski et al., 1999).

Prophylaxis of manic and depressive episodes

In bipolar disorders, maintenance studies are used to evaluate the ability of a mood stabilizer to prevent relapse and recurrence of further episodes. However, there is an overall lack of consensus on methodology for this type of study (Calabrese et al., 2001). The difficulties that clinicians have experienced in repeating the long-term lithium response rates achieved during the 1960s and 1970s illustrates the general methodological problems associated with conducting maintenance studies for bipolar disorder. Changing diagnostic criteria and study designs, heterogeneous samples, and concomitant medication use are among the main factors affecting outcomes.

Current American Psychiatric Association guidelines recommend carbamazepine as an alternative to lithium in the maintenance treatment of bipolar disorder (Hirschfeld et al., 2002). The prophylactic effects of carbamazepine have been suggested by an overall response rate of 63% from 14 controlled or partially controlled studies (ranging from 9 months to 3 yr duration), which is similar to that reported for lithium. The effect of carbamazepine was approximately equal for manic and depressive episodes (reviewed in Post et al., 1996b). Eight of the 14 prophylaxis studies were controlled, including placebo-controlled parallel group, randomization to carbamazepine or lithium and cross-over with randomization to carbamazepine or lithium. Three controlled studies (Denicoff et al., 1997; Luszcz et al., 1988; Watkins et al., 1987) permitted adjunctive treatment as necessary, and patients were refractory to lithium in all studies except Coxhead et al. (1992). Further details of these studies are presented in Table 2.

The prophylactic efficacy of carbamazepine was similar to that of lithium in six of the eight controlled studies (Coxhead et al., 1992; Denicoff et al., 1997; Luszcz et al., 1988; Placidi et al., 1986; Watkins et al., 1987), and superior to placebo in one study (Okuma et al., 1981) (Table 2).

In the largest of the controlled studies, carbamazepine (635 ± 190 mg/d) was compared with lithium

(26.8 ± 6.76 mmol/l) in 171 patients with bipolar I and bipolar II disorder over 2.5 yr. The study was notable both in terms of its size and the fact that two categories of bipolar I patients were analysed, 'classical' and 'non-classical' (Greil and Kleindienst, 1999; Greil et al., 1997, 1998; Kleindienst and Greil, 2000, 2002). The efficacy of lithium and carbamazepine were found to be similar in bipolar II disorder patients, but showed differences in bipolar I patients. In 'classical' bipolar I patients (no comorbidity or mood-incongruent delusions), there was a significant advantage for lithium in terms of hospitalization rates (26% vs. 62%, $p=0.012$). In 'non-classical' patients (all other patients), there was a tendency for carbamazepine to be superior (31% vs. 44%, $p=0.34$) (Kleindienst and Greil, 2000). These findings suggest that carbamazepine may be more suited for the large number of patients with 'non-classical' disease than lithium (Kleindienst and Greil, 2000). This apparent superiority of carbamazepine over lithium in treating atypical disease and mixed states has been noted elsewhere (Hellewell, 2002) and is supported by limited evidence that carbamazepine has some efficacy in treating rapid cycling.

Although Kleindienst and Greil (2002) found a trend in favour of lithium for suicidal behaviour, carbamazepine was superior to lithium in terms of patient satisfaction. Considering the whole patient population, inter-episodic symptomatology and re-hospitalization rates (confirmed by survival analysis) were similar for both treatments (Figure 2), although a higher proportion of patients could be judged to have a 'good clinical response' for lithium than for carbamazepine (40% vs. 24% respectively) (Kleindienst and Greil, 2002).

Lithium (up to $0.6 \mu\text{mol/l}$) and carbamazepine (up to $40 \mu\text{mol/l}$) were also found to have comparable long-term efficacy in bipolar and unipolar patients in three open-label studies ranging from 1.2 to 2.0 yr duration (Bellaire et al., 1990; Cabrera et al., 1987; Simhandl et al., 1993). Furthermore, Stuppaeck et al. (1990) found that 20 out of 24 (83%) bipolar and unipolar depressive patients treated for 20.2 months with carbamazepine (mean dose 600–800 mg/d) could be judged to have experienced 'substantial benefit'. Overall, these lithium-refractory patients showed a significant reduction from 2.27 to 0.75 in yearly depressive episodes ($p<0.0001$).

Tolerability

Carbamazepine induces cytochrome P450 enzyme activity which can lead to decreases in the blood levels of some commonly used medications (Table 3).

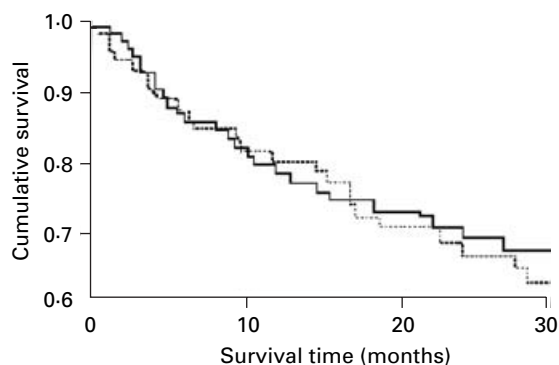
Table 2. Controlled trials of carbamazepine in the prophylaxis of bipolar disorders

Study	Design	Duration	Treatment (daily dose, mg)	Patients [mean age (range), yr]	Outcome measures	Responders
Okuma et al. (1981)	r, db, pc	1 yr	CBZ (200–1250) vs. placebo	22 bipolar [43 (21–64)]	RSMD-J	6 (60%) CBZ, 2 (22%) placebo
Placidi et al. (1986)	r, db	3 yr	CBZ (400–1600) vs. Li (300–1200)	83 (54 bipolar, 29 schizoaffective) (41 ± 12)	BPRS, CGI	≥2/3 of patients in each group
Watkins et al. (1987)	r, db	1.5 yr	CBZ (5–12 µg/ml) vs. Li (0.4–0.9 mmol/l)	52 bipolar or unipolar (20–60)	Global assessment	16 (43%) CBZ, 15 (41%) Li
Lusznat et al. (1988)	r, db	Up to 1 yr	CBZ (serum level 6–12 mg/l) vs. Li (serum level 0.6–1.4 mmol/l)	54 (52 bipolar, 2 schizoaffective) (age na)	HRSD, BRMRS	9 (33%) CBZ, 5 (19%) Li
Small et al. (1991)	r, db	Up to 2 yr	CBZ (700–1036) vs. Li (1035–1278)	16 bipolar [39 (22–73)]	SDMS-D&M, YMRS, BPRS, CGI	8 (33%) patients in each group were considered responders and remained in the study for up to 2 years. Average stay after week 8 was 9.1 wk for CBZ and 14.9 wk for Li
Coxhead et al. (1992)	r, db	1 yr	CBZ (serum levels 38–51 mmol/l) vs. Li (serum levels 0.6–1.0 mmol/l)	31 bipolar (48 ± 12)	BRMRS, HRSD	7 (47%) CBZ, 7 (44%) Li
Denicoff et al. (1997)	Year 1: r, db; Year 2: co, db; Year 3: db Years 1 and 2: Li or CBZ monotherapy Year 3: Li and CBZ combination therapy (CBZ=up to 1600 mg/d; Li=serum levels of 0.5 to 1.2 mmol/l)			52 bipolar (41 ± 11)	LCM-p, BDI, MSSTAI, HRSD, YMRS, RSDM	11/35 (31%) CBZ, 14/42 (33%) Li, 16/29 (55%) CBZ + Li
Kleindienst and Greil (2000, 2002)	r	2.5 yr	CBZ (635 ± 190 mg/d) vs. Li (26.8 ± 6.76 mmol/l)	171 bipolar (114 bipolar I, 57 bipolar NOS) (40 ± 13)	Re-hospitalization Inter-episodic symptomatology Global assessment	Failure rate 50% higher for CBZ vs. Li in bipolar I patients. In bipolar II patients, CBZ at least as effective as Li, with an advantage over Li in bipolar NOS patients of 7% vs. 37% (failure rates)

Abbreviations: r, randomized; db, double blind; pc, placebo controlled; co, cross-over; CBZ, carbamazepine; Li, lithium; RSMD-J, Rating Scale for Mania and Depression from the Clinical Psychopharmacology Research Group in Japan; BRMRS, Bech–Rafaelson Mania Rating Scale; HRSD, Hamilton Rating Scale for Depression; LCM-p, prospective daily life charting using the NIMH chart method and manual; BDI, Beck Depression Inventory; MSSTAI, Modified Spielberger State-Trait Anxiety Inventory; YMRS, Young Mania Rating Scale; RSDM, Raskin Severity of Depression and Mania scale; SDMS-D&M, manic subsection of the Depression and Mania Scale; BPRS, Brief Psychiatric Rating Scale; CGI, Clinical Global Impression Scale; NOS, not otherwise specified.

Table 3. Drug–drug interactions of mood stabilizers

Mood stabilizer	Main drug–drug interactions
Lithium	<ul style="list-style-type: none"> • The anti-inflammatories indomethacin and piroxicam can increase serum lithium to toxic levels • Metronidazole can lead to lithium toxicity through decreased renal clearance • Use of calcium channel blockers with lithium may induce neurotoxicity • Urea, xanthine preparations and alkylating agents such as sodium bicarbonate can lower serum lithium concentrations
Carbamazepine	<ul style="list-style-type: none"> • Serum levels of carbamazepine are substantially reduced by co-administration of phenobarbital, phenytoin or primidone • Carbamazepine significantly shortens the half lives of phenytoin, warfarin, doxycycline, and theophylline • Levels of haloperidol and divalproex are reduced by co-administration with carbamazepine • Concomitant administration of lithium and carbamazepine may induce neurotoxic effects • Carbamazepine may adversely effect the efficacy of oral contraceptives
Oxcarbazepine	<ul style="list-style-type: none"> • Oxcarbazepine increases the metabolism of dihydropyridine calcium antagonists and oral contraceptives, resulting in lower serum concentrations • Plasma levels of phenytoin may increase by up to 40% at higher doses of oxcarbazepine (1200 mg/d or more) • Strong inducers of cytochrome P450 enzymes (e.g. carbamazepine, phenytoin, phenobarbital) can decrease plasma levels of the active component of oxcarbazepine
Divalproex	<ul style="list-style-type: none"> • Divalproex-free fraction may increase up to 4-fold in the presence of aspirin • Felbamate increases divalproex concentration by 35% • Rifampicin increases oral clearance of divalproex by 40%
Lamotrigine	<ul style="list-style-type: none"> • Reduces plasma concentrations of divalproex by 25% • Divalproex increases lamotrigine concentration by 50% • Carbamazepine decreases lamotrigine concentration by 50% • Inhibits dihydrofolate reductase; therefore caution is required in administering other medications that inhibit this enzyme

**Figure 2.** Re-hospitalization survival analysis for carbamazepine (.....) and lithium (—) prophylaxis over 2.5 years of treatment (adapted from Kleindienst and Greil, 2002, with permission).

The adverse events reported by patients in the studies of carbamazepine discussed here are in line with the known safety profile of this agent. The major metabolite of carbamazepine is carbamazepine-10,11-epoxide, and this is thought to be the cause of many associated side-effects. Carbamazepine is generally well tolerated, but can result in side-effects such as vertigo, somnolence, ataxia, and fatigue (Novartis Pharmaceuticals, 2002). Therefore, treatment should be initiated at low levels and titrated gradually as side-effects and clinical response permit. Rash occasionally develops and should be monitored closely. Transient leukopenia occurs in $\geq 10\%$ of patients receiving carbamazepine, and thrombocytopenia is present in 1–10% of patients (Novartis Pharmaceuticals, 2002). The risk of aplastic anaemia and agranulocytosis is 5–8 times greater for patients receiving

carbamazepine than for the general population (Novartis Pharmaceuticals, 2002).

Oxcarbazepine

The new-generation anticonvulsant oxcarbazepine has been marketed in the USA since 2000 and is approved worldwide as both monotherapy and as combination therapy in adults and children with partial seizures (Novartis Pharmaceuticals, 2001). As stated previously, oxcarbazepine is structurally related to carbamazepine and may be expected to have similar efficacy to carbamazepine in the treatment of various disorders. In the treatment of seizures, oxcarbazepine shows equivalent efficacy to carbamazepine and other first-line agents, although oxcarbazepine has an improved safety profile and a reduced potential for drug–drug interactions (Bill et al., 1997; Christe et al., 1997; Dam et al., 1989; Grant and Faulds, 1992). Several studies have suggested that oxcarbazepine may be useful as an antimanic agent. Data from controlled studies of oxcarbazepine in the treatment of acute mania are limited, with most of the data coming from open studies or retrospective reviews of patients' charts (Table 4).

Controlled studies

The four randomized controlled studies that have been conducted to date have suggested that oxcarbazepine is superior to placebo (Emrich et al., 1983), and may have similar efficacy to lithium (Emrich, 1990), valproate (Emrich et al., 1984, 1985) and haloperidol (Emrich, 1990; Müller and Stoll, 1984) in acute mania (Table 4).

The first evaluation of oxcarbazepine in affective disorders was a small (six patients) double-blind, placebo-controlled study in acute mania which resulted in improvements of approx. 50% on the Inpatient Multidimensional Scale (1800–2100 mg/d doses) and few adverse events (dizziness and vertigo with 2100 mg/d) (Emrich et al., 1983).

The same group then conducted two double-blind trials in acute mania comparing oxcarbazepine with lithium and haloperidol. In the first study, both lithium (24 patients, 1100 mg/d) and oxcarbazepine (28 patients, 1400 mg/d) reduced Bech–Rafaelson Mania Rating Scale (BRMRS) scores substantially and to a similar extent at doses considered standard to low (Figure 3). An oxcarbazepine dose of 1400 mg/d corresponds to a carbamazepine dose of only approx. 900 mg/d. Adverse events were slightly higher in the oxcarbazepine group, although tolerability of oxcarbazepine and lithium was rated to be similar by the

physician's global evaluation (Emrich, 1990). In a second randomized study conducted by Emrich et al. (1983), 38 patients with acute mania received either oxcarbazepine (mean dose of 2400 mg/d) or haloperidol (mean dose of 42 mg/d), and improvements on the BRMRS were similar over 2-wk treatment (Figure 4). However, oxcarbazepine demonstrated significantly better tolerability despite the relatively high dose used, with 35% of haloperidol patients developing side-effects, compared to 10% of oxcarbazepine patients. These findings suggest that oxcarbazepine is effective in treating acute mania, since high haloperidol doses were used to achieve similar improvements to oxcarbazepine (Emrich, 1990).

Müller and Stoll (1984) studied a group of 20 patients with mania who received oxcarbazepine (900–1200 mg/d) or haloperidol (15–20 mg/d) for 2 wk. They observed a faster onset of action with oxcarbazepine, although the two treatments both reduced BRMRS scores by approx. 50% and had similar tolerability.

Open studies

Five open-label studies have investigated oxcarbazepine use in bipolar disorder (Table 4). Müller and Stoll (1984) treated 48 patients experiencing manic symptoms with relatively high doses of oxcarbazepine (up to 3000 mg/d). Over 80% of patients showed a good response, and over 90% experienced good tolerability (Müller and Stoll, 1984). In 10 patients with manic syndromes or schizoaffective psychosis, Velikonja and Heinrich (1984) investigated the effect of oxcarbazepine treatment (900 mg/d) and antipsychotics, compared to a matched control group who were not receiving oxcarbazepine. Treatment with oxcarbazepine was associated with around half the level of antipsychotic use (Velikonja and Heinrich, 1984).

Oxcarbazepine was administered to 12 patients with mania in 2-wk periods, divided by 1 wk with no medication. In patients with mild to moderate mania, oxcarbazepine (300–2400 mg/d) was as effective as monotherapy, with 33% of patients meeting the defined response criteria of a 50% or more improvement on the YMRS. Although this was a small, open-design trial with no placebo use during the off period, oxcarbazepine was found to have efficacy in patients with low to moderate manic episodes but it is unclear how efficacious oxcarbazepine would be in treating patients with severe mania (Hummel et al., 2002).

Two studies found that oxcarbazepine may be effective as add-on therapy in treating patients with bipolar disorder who exhibit both acute manic and depressive symptoms (Table 4) (Benedetti et al., 2004;

Table 4. Studies of oxcarbazepine in the treatment of bipolar disorders

Study	Design	Duration	Treatment (daily dose, mg)	Patients [mean age (range), yr]	Outcome measures	Responders
Controlled studies						
Emrich et al. (1983)	db, pc	na	OXC (1800–2100) vs. placebo (na)	6 acutely manic	IMPS	20–90% improvement in IMPS score
Müller and Stoll (1984)	r	2 wk	OXC (900–1200) vs. HAL (15–20) (na)	20 manic	BRMRS	Decrease of around 20 points on the BRMRS (around 50%) for OXC and HAL
Emrich et al. (1984, 1985)	db, pc, variable placebo/drug design	na	OXC (1800–2100) vs. VAL (1800–3800)	OXC 7, VAL 5 all have manic syndromes	IMPS	OXC IPMS reduction by $49.9\% \pm 26.1\%$ VAL IPMS reduction by $49.6\% \pm 36.6\%$
Emrich (1990)	r, db	2 wk	OXC (up to 1400) vs. Li (up to 1100)	52 acutely manic (na)	BRMRS, Global assessment	A similar improvement of >50% in BRMRS score Tolerability rated as similar for OXC and Li
Emrich (1990)	r, db	2 wk	OXC (2400) vs. HAL (42)	38 acutely manic (na)	BRMRS, Global assessment	Around 50% decrease in BRMRS score for both OXC and HAL 94% patients rated as experiencing good or excellent tolerability with OXC vs. 84% for HAL
Open studies						
Müller and Stoll (1984)	Pilot study	Median 39 days (10–86)	OXC (600–3000)	48 manic [41 (17–61)]	na	83% patients judged to experience a 'good' or 'very good' therapeutic effect
Velikonja and Heinrich (1984)	Pilot study	na	OXC (900)	10 manic or schizoaffective (na)	Global assessment	Decrease of psychotic symptoms in all patients. Dose of concomitant neuroleptic required was significantly reduced
Hummel et al. (2002)	On-off-on	2 wk OXC, 1 week no therapy, 2 wk OXC	OXC (300–2400)	12 manic (na)	YMRS	33% showed good response ($\geq 50\%$ reduction in YMRS score)
Munoz (2002)	Prospective, single centre	12 wk	OXC (300–2400)	28 bipolar (21 manic, 7 depressed) (18–65)	YMRS HRSD	71% manic patients showed $\geq 50\%$ response on YMRS 100% depressed patients showed $\geq 50\%$ on HRSD
Benedetti et al. (2004)	Pilot add-on study	8 wk, 4–12 month follow-up	OXC (mean 919 ± 336)	18 bipolar (4 manic, 8 depressed, 8 with mixed episodes)	CGI-BP, BPRS, BRMRS	61% (11/18) patients considered responders (CGI-BP score of 1 or 2). In addition, 33% and 61% patients were responders ($\geq 50\%$ improvement) on the BPRS and BRMRS, respectively

Chart review studies

Ghaemi et al. (2003)	rcr	Mean exposure of 16 wk	OXC (mean 1057)	42 bipolar (25 type I, 4 type II, 13 NOS) [33 (13–59)]	CGI	Positive response in 57% patients overall, and 68% for those receiving OXC ≥ 4 wk
Ghaemi et al. (2002)	rcr	Mean exposure 11 wk	OXC (mean 592)	13 bipolar [44 (22–59)]	CGI	Mild improvement in 46% (6/13) patients Moderate improvement in 16% (2/13) patients
Nasr and Casper (2002)	rcr	≥ 4 wk	OXC (300–2400)	87 with affective disorders, 28 bipolar (41 [13–72])	CGI, VAS, CDRS	Significant improvement from baseline in CGI score for all patients ($p < 0.0001$) Bipolar patients also showed a significant improvement from baseline in VAS score (mean change of 0.018, $p = 0.028$)
Munasifi et al. (2002)	rcr	na	OXC (mean 488)	97 bipolar, 35 type I, 41 type II, 21 mixed [36 (5–74)]	Zeigler, HRSD	12 point decrease in Zeigler score 22 point decrease in HRSD score

Abbreviations: r, randomized; db, double blind; pc, placebo controlled; rcr, retrospective chart review; OXC, oxcarbazepine; HAL, haloperidol; Li, lithium; IMPS, Inpatient Multidimensional Psychiatric Scale; CDRS, Carroll Depression Rating Scale; CGI, Clinical Global Impression Scale; CGI-BP, Clinical Global Impression Bipolar Version Scale; VAS, Visual Analogue Scale; BPRS, Brief Psychiatric Rating Scale; BRMRS, Bech–Rafaelson Mania Rating Scale; HRSD, Hamilton Rating Scale for Depression; YMRS, Young Mania Rating Scale.

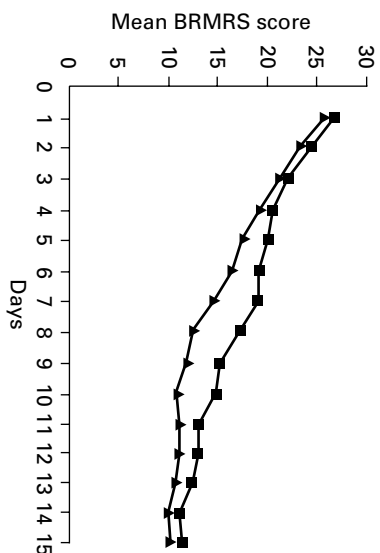


Figure 3. Mean mania rating scale values during 15 days of oxcarbazepine (■, $n = 24$) or lithium (▲, $n = 28$) therapy (adapted from Emrich, 1990, with permission), BRMRS, Bech–Rafaelson Mania Rating Scale.

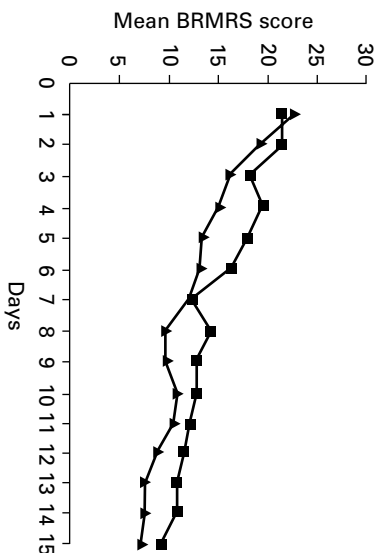


Figure 4. Mean mania rating scale values during 15 days of therapy with oxcarbazepine (■, $n = 19$) or haloperidol (▲, $n = 19$) (adapted from Emrich, 1990, with permission), BRMRS, Bech–Rafaelson Mania Rating Scale.

Munoz, 2002). In a 12-wk open-label study of 28 patients (21 initially manic, 7 initially depressed) receiving 300–2400 mg/d oxcarbazepine, 71% (15/21 manic patients) experienced a $\geq 50\%$ response on the YMRS, and all (7/7) depressed patients showed a $\geq 50\%$ response on the HRSD. Most patients took concomitant mood stabilizers or antipsychotics, but by the end of the study, mood stabilizer use had decreased by 27%. No association was found between oxcarbazepine treatment and weight gain (Munoz, 2002). A second study examined 18 patients (16 currently manic, 2 depressive) who had not achieved an adequate response to lithium. After 8-wk treatment with oxcarbazepine in addition to existing lithium therapy, the mean dose of oxcarbazepine was 919.4 mg/d. Eleven patients (61%) were

considered responders, having a Clinical Global Improvement (CGI) score of 1 or 2 at week 8, seven (64%) of which remained stable during the entire follow-up period (4–12 months). A major limitation of this study was the concomitant use of antipsychotics. However, the findings suggest the potential of oxcarbazepine as adjunctive therapy to lithium in both the acute and long-term treatment of bipolar disorder (Benedetti et al., 2004).

In support of these findings from conventional clinical studies, four retrospective chart reviews have recently supported the efficacy of oxcarbazepine in treating mood disorders (Ghaemi et al., 2002, 2003; Munasifi et al., 2002; Nasr and Casper, 2002). The records of 239 bipolar patients were analysed in these studies, the majority of whom were refractory with other mood stabilizers. Mean daily doses of oxcarbazepine ranged from 488 mg to 1057 mg. Responses were encouraging, with many patients showing a good antimanic effect even with the relatively low oxcarbazepine dose of 488 mg/d (Table 4).

Tolerability

Unlike carbamazepine, oxcarbazepine undergoes predominantly reductive metabolism and, therefore, only minimally affects the majority of the cytochrome P450 (oxidative) enzymes, resulting in a low potential for drug–drug interactions (Grant and Faulds, 1992). However, oxcarbazepine can induce the cytochrome P450 enzymes CYP3A4 and CYP3A5, which are involved in the metabolism of both dihydropyridine calcium antagonists and oral contraceptives, resulting in lower plasma concentrations of these drugs (Fattore et al., 1999). The main drug–drug interactions of oxcarbazepine and other mood stabilizers are shown in Table 3.

The most commonly reported adverse events for oxcarbazepine are those affecting the central nervous system, including fatigue, dizziness, and headache. In the studies investigating its efficacy in bipolar disorder, oxcarbazepine was generally well tolerated, with most adverse events being mild to moderate in severity and in line with the known safety profile of the drug (e.g. somnolence, dizziness, nausea). The risk of leukopenia, aplastic anaemia, agranulocytosis, and elevated liver function tests is not significantly increased with oxcarbazepine. Treatment-emergent hyponatremia, defined as a serum sodium level <125 mmol/l (Kumar and Berl, 1998), has been reported in 3% of patients receiving oxcarbazepine in clinical trials (Glauser, 2001). In comparison, hyponatremia has been observed in between 4.8% and 40% of

patients treated with carbamazepine (Van Amelsvoort et al., 1994).

Discussion

There is good evidence to support the use of carbamazepine in the acute treatment of bipolar disorders. The efficacy of carbamazepine in acute mania is broadly comparable to that of lithium, valproate, and antipsychotics, and there is evidence of additional effectiveness in patients with atypical or mixed presentations. There is also some support for the use of carbamazepine in treating depressive episodes and as maintenance therapy, although further controlled studies with greater numbers of patients are required to confirm these findings.

A growing body of data suggests that oxcarbazepine may have similar efficacy to carbamazepine in treating mania and may have mood-stabilizing properties. These data, plus oxcarbazepine's association with carbamazepine, has led the American Psychiatric Association, in its treatment guidelines, to recommend oxcarbazepine in the acute and maintenance treatment of bipolar disorder. The safety and tolerability profile of oxcarbazepine make it an attractive alternative to other treatment options.

Furthermore, most bipolar patients will be receiving other medications (commonly three or more), and therefore a well-tolerated agent such as oxcarbazepine, which demonstrates few drug–drug interactions, is preferable to an older anticonvulsant (Frye et al., 2000). The data for oxcarbazepine in prophylaxis or depressive episodes are limited; large, controlled studies are needed to confirm the preliminary findings of several smaller studies (Cabrera et al., 1987; Wildgrube, 1990). In a recent study involving 20 patients with affective or schizoaffective disorders, patients receiving oxcarbazepine had their average annual episode duration and average annual rate of episodes reduced by 45.8% and 34.8% respectively (Kouzavkova et al., 2000). In addition, 82.2% of patients had a good or moderate response, and there was a negative correlation between prophylactic efficacy and the speed of individual oxcarbazepine biotransformation.

Ketter and Calabrese (2001) have recently highlighted the fact that the treatment of mania has overshadowed research into treating other areas of importance in bipolar disorder. They have suggested that bipolar disorder should be considered as a deviation from 'baseline' mood/behaviour. Thus 'above baseline' (treated by class A agents) is characterized by mania and other degrees of mood elevation, and

'below baseline' (treated by class B agents) is defined as depression. These definitions are useful, as they assist in the understanding of how mood stabilizers, particularly in a large drug class such as the anti-convulsants, differ from each other. Reviewing the clinical data shows that lithium comes closest to being a mood stabilizer that works both from 'above' and 'below', while lamotrigine, another newer anti-convulsant, is probably a class B agent. Carbamazepine and oxcarbazepine can be considered class A agents, although there is some evidence for the positive effect of carbamazepine in depression. It is hoped that by examining the efficacy of different combinations of agents from these newly defined classes, more effective approaches to the individual management of patients will be developed.

In reviewing available carbamazepine data, Brambilla et al. (2001) concluded that carbamazepine should be considered for lithium-resistant or lithium-intolerant patients. Others have noted the improved efficacy of lithium and carbamazepine as combination therapy, compared to monotherapy with either agent (Denicoff et al., 1994; Di Costanzo and Schifano, 1991; Kishimoto, 1992). By extension, the lack of drug-drug interactions with oxcarbazepine, together with equivalent efficacy, suggest that oxcarbazepine may be more convenient to use than carbamazepine in combination therapy. In addition, carbamazepine has proven efficacy in both acute and maintenance treatment of bipolar disorders, and unlike lithium, may be particularly effective in patients presenting with atypical disease and rapid cycling. This suggests that oxcarbazepine potentially has a wider role in the treatment of bipolar disorder. However, further controlled data are essential to support the preferential use of carbamazepine or oxcarbazepine in the treatment of atypical disease and prophylaxis, compared to conventional treatments such as lithium, valproate, or atypical antipsychotics.

Acknowledgements

The authors received editorial support from Novartis Pharmaceuticals in the production of this manuscript.

Statement of Interest

Dr Hirschfeld has received grant/research support from Abbott Laboratories, Bristol-Myers Squibb, GlaxoSmithKline, Organon Inc., and Wyeth-Ayerst; has served as a consultant or on the advisory board for Abbott Laboratories, AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Forest Laboratories, Eli

Lilly & Company, Pfizer, Inc., Organon, Inc., Janssen Pharmaceutica, Wyeth-Ayerst, Novartis, and UCB Pharma; and has served on the speakers' bureau for Abbott Laboratories, and Forest Laboratories. Dr Kasper has received grant/research support from Eli Lilly, Lundbeck, Bristol-Myers Squibb, GlaxoSmithKline, Organon, and Servier; has served as a consultant or on the advisory board for AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Eli Lilly & Company, Lundbeck, Pfizer, Inc., Organon, Inc., Janssen Pharmaceutica, and Novartis; and has served on the speakers' bureau for AstraZeneca, Eli Lilly, Lundbeck, and Janssen Pharmaceutica.

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