

## Rapid Cyclers, Temperament, and Antidepressants

A. Kukopoulos, B. Caliari, A. Tundo, G. Minnai, G. Floris, D. Reginaldi, and L. Tondo

THE GENERAL IMPRESSION of clinicians today is that the course of recurrences of manic-depressive illness has substantially changed in the last 20 yr. The recurrences of many patients have become more frequent. One sees more manias and hypomanias and therefore more bipolar cases than before, more rapid cyclers, and more chronic depressions. It is difficult to verify and quantify all these changes, because comparisons in psychiatry, especially among statistical data gathered over long time intervals, are very hard to make. Nevertheless, reading the older literature, one has a clear impression that the course of the disease was different then.

In his monograph on *la folie à double forme*, Ritti<sup>1</sup> presented only 17 cases with a rapid course; he collected them from various French and German authors. Kraepelin illustrated one case with a rapid cycling course in his graphs of type of course. This was case C, and he commented, "I had to seek for a long time in my cases until I finally found at least one course of the type that case C represents."<sup>2</sup> J. Lange speaks of only one patient with two cycles per year.<sup>3</sup> Brodwall found only two circular cases among 110 patients.<sup>4</sup> Lundquist referred to only "a few cases" with circular courses among 319 manic-depressive patients.<sup>5</sup> Stenstedt found only one case of circular psychosis among 216 manic-depressive patients.<sup>6</sup> Many authors do not mention rapid courses at all. Today, on the contrary, rapid courses have become a frequent and serious therapeutic problem.

The investigation of the course of manic-depressive illness is a difficult task in itself, and the investigation of possible factors that influence this course is extremely difficult. Yet the above-mentioned changes and the general increase of depressions today make this investigation necessary. Of all the possible factors that unfavorably influence the course of the disease what most urgently need to be studied are the treatments themselves—first, because they certainly influence the disease, and second, because treatments are given by the doctor and therefore can be easily modified. This is certainly not the case of other factors like menopause, older age, life situations, and so forth.

During the first years of the use of antidepressant drugs some papers appeared that indicated a clear increase of recurrences in comparison to the previous course treated with electroconvulsive therapy (ECT) or otherwise. We draw attention to the work of Freyhan,<sup>7</sup> Lauber,<sup>8</sup> Arnold and Kryspin-

---

*From the Centro Lucio Bini, Rome and Cagliari, Italy.*

A. Kukopoulos, M.D., B. Caliari, M.D., A. Tundo, M.D., G. Minnai, M.D., G. Floris, M.D., D. Reginaldi, M.D., L. Tondo, M.D., *Centro Lucio Bini, Rome and Cagliari, Italy.*

*Address reprint requests to A. Kukopoulos, M.D., Centro Lucio Bini, Via Crescenzo 4, 00193 Roma, Italia.*

*© 1983 Grune & Stratton, Inc. 0010-440X/83/2403/0007/\$1.00/0*

Exner,<sup>9</sup> and Hoheisel.<sup>10</sup> The last of that series of reports was the good work of Till and Vučković.<sup>11</sup> But these studies were neglected, while on the contrary much work has been done to establish a possible preventive effect of anti-depressant drugs. The results of the trials on the prophylactic effect of the antidepressants are controversial. The general opinion today is that antidepressants given as a maintenance treatment are beneficial in monopolar depressive cases, but may trigger manias and hypomanias in bipolar cases. The recent reports of Siris et al.,<sup>12</sup> Wehr and Goodwin,<sup>13</sup> and Lerer et al.,<sup>14</sup> although they concern a small number of patients, clearly indicate the possibility that tricyclic antidepressants can induce rapid cycling.

In this paper, as in a previous study by our group,<sup>15</sup> we study the onset of rapid cyclicity and the influence of treatments on it. We also try to determine which patients are likely to become rapid cyclers.

#### PATIENTS AND METHOD

Due to the difficulties of the investigation of the course of the disease and its changes, we chose to study a gross change, namely, the change to rapid cyclic course. Following Dunner and Fieve,<sup>16</sup> we consider as rapid cycling a course with four or more affective episodes a year. It can also be defined as a course with two or more cycles a year. Unipolar rapid cyclers are rare and are probably only apparently unipolar.

Among our manic-depressive patients we found a rapid cycling course in 118 cases whose previous course could be reliably reconstructed. Thirty-two of them were rapid cyclers from the beginning of their illness. The other 86 had at first a different course, which later changed into rapid cyclic. We divided the course of the disease into two parts: the course from the first episode until the onset of rapid cyclicity and the course after rapid cyclicity was established.

In most of our cases the investigation of the previous course and of the change to rapid cyclicity was based on information gathered from the patients themselves, their families, and available medical records. The rapid cyclic course itself was accurately determined, because the patients were then under our care and were part of this study, which began 4 yr ago. The length of episodes and the length of free intervals of the course prior to rapid cyclicity were measured with some inevitable approximation, which, however, is acceptable in view of the method of this study, which compares the rapid cyclic course and the course prior to it. As will be seen in the results, the difference of length of episodes and length of free intervals is so large that the approximate determinations of length in the previous course cannot invalidate the results.

The detection of mild hypomania in the past is more problematic. It may well be that some cases that we classified as unipolar depressive in their previous course did have mild hypomanic episodes that were not noticed by the patient or his or her family, and could not be recollected as such later. This, too, does not compromise the main results of our study, which is primarily concerned with the acceleration of the course of the disease and only secondarily with the transformation of a unipolar to a bipolar course.

Every effort was made to establish the treatments these patients received during their previous episodes: Hospital records and prescriptions were the basis of this information. Patients' recollections and family reports were accepted whenever they seemed reliable. The compliance of the patients to the prescribed medication cannot be monitored retrospectively, which is a shortcoming of our method.

We recorded as depressive phases those episodes in which the depressive symptoms required hospitalization or outpatient treatment or which impaired the patient's working and social activities.

We recorded as hypomanias those episodes characterized by elevated mood or irritability, hyperactivity, and decreased need of sleep, but the patients' behavior was not disturbed enough to require hospitalization.

We recorded as manias those episodes of psychomotor excitement that required hospitalization.

## RESULTS

### Rapid Cyclicity From the Beginning

Thirty-two patients (10 men and 22 women) had a rapid cyclic course from the beginning. The age at first episode was 40.2 and 37.6 yr, respectively, and the disease had lasted 4.8 and 6.7 yr. The number of episodes per year was 8 and 7.7, respectively. Three patients (1 man and 2 women) had a unipolar depressive course, 26 (8 men, and 18 women) had a bipolar II (BPII) course, and 3 (1 man, and 2 women) had a bipolar I (BPI) course.

### Rapid Cyclicity With a Different Previous Course

Eighty-six patients (26 men and 60 women) had a different course before becoming rapid cyclers. This previous course had lasted 12.6 yr for men and 9.7 yr for women. The rapid cyclic course had lasted 4.6 and 4.4 yr, respectively. The number of episodes per year during the previous course was 0.8 for men and 0.7 for women. The number of episodes per year during the rapid cyclic course was 6.8 and 7.0, respectively.

The great difference in frequency of recurrences between the previous course and the rapid cyclic course of these patients is remarkable. The average age at first episode was 31 for both men and women, and the average age at onset of rapid cyclicity was 43 and 41, respectively. It is noteworthy that these last two ages are close to the average age at the first episode of the cases that were rapid cyclers from the beginning (42.4 for men, and 37.6 for women).

The polarity of the course of these 86 rapid cyclers was: 6 (1 man and 5 women) were unipolar depressive, 65 (17 men and 48 women) were BPII, and 15 (8 men and 7 women) were BPI. In their previous course, 42 patients (12 men and 30 women) had two or more depressions, 28 (6 men and 22 women) had a depression-hypomania course, and 16 (8 men and 8 women) had other types of bipolar cycles.

Different from our previous work,<sup>15</sup> in the present study, we consider the depression after which rapid cyclicity started as part of the previous course; indeed, it occurred after a long interval and rapid cyclicity started afterward. It should be added that in the majority of the original unipolar cases, the later depressions were followed by hypomania, and then rapid cyclicity was eventually established. The large percentage of cases with an initial depression-hypomania cycle or that were transformed into this type of cycle before becoming rapid cyclers should be emphasized. This type of cycle is the predominant one before and during rapid cyclicity.

### Antidepressant Drugs and the Change of Course

In the majority of cases the change of the previous course into rapid cyclic coincided with antidepressant drug treatments. All the current antidepressant drugs (MAOI, tricyclics, tetracyclics, sulpiride, nomifensin, and mianserin) were found to have coincided with the beginning of rapid cyclicity. Fifty-two patients (12 men and 40 women) had no specific antidepressant drug treatments

during their previous episodes: they had psychotherapy or mild anxiolytics or their episodes had been treated only with ECT or they had no treatment at all.

The number of episodes during the previous period of the disease was 0.8 per year, whereas after the beginning of treatments with antidepressant drugs the number of episodes was 6.5 per year.

In 17 cases drug treatments were maintained over one or more free intervals. In 33 cases the transformation of the course took place within the first year after antidepressant drugs were begun; in 14 cases, during the second year; and in 5 cases, after longer periods (3, 3, 3, 6, 10 yr) of repeated or continuous drug treatment. We include these last 5 cases because their previous course without antidepressants consisted of long depressive episodes and long free intervals. The gradual increase of the frequency of episodes and the shortening of the episodes and intervals occurred during treatments with high doses of antidepressants and high maintenance doses during the free intervals.

In 15 women the change of the course coincided with menopause.

The common feature of the transformation of previous courses into rapid cyclic ones was the appearance for the first time in the course of the disease of a hypomanic episode after the depression, or the accentuation of a hypomania that had been of a milder intensity in previous recurrences. It was after one or more such depression-hypomania cycles (more rarely, depression-mania) that the following depression occurred without interval and that continuous circularity was established.

#### PREMORBID TEMPERAMENT

When we studied the patients with rapid cyclic course, we were impressed by their premorbid temperament: in fact, most of them were hyperthymic or cyclothymic. We therefore decided to collect all possible information about the temperament of our patients before the onset of their illness. Thus, our study is entirely retrospective and is based on descriptions given by the patient and his or her family. We investigated the temperament in its two basic components—drive and mood. In this we follow Kretschmer<sup>17</sup> and consider these two components as varying between the two poles of high and low drive and high and low mood. We evaluated drive by amount and variety of working activity, range of interests, ambition, degree of liveliness, and general life-style. Mood was established through descriptions of prevailing mood, tendency toward optimism or pessimism, and degree of expansiveness.

We classified temperament as cyclothymic, hyperthymic, normothymic, and dysthymic. This corresponds to the classical typology of Kraepelin and Schneider. While they describe pathologic affective temperaments and personalities, we refer to conspicuous variations of drive and mood that do not necessarily result in abnormal behavior. Indeed, the majority of our patients were considered as having normal personalities, although their temperamental traits were noticeable.

#### Cyclothymic Temperament

People with a cyclothymic temperament were those who had clear, sustained oscillations of drive and mood that can last hours, days, or months but which

never reach the prolonged severity of an affective episode. Oscillations of long duration may have a seasonal pattern, the most frequent of which are elevated mood and drive in spring and summer and lowered mood and drive in autumn and winter. These highs and lows are often reflected in scholastic attainment. When clear-cut manic-depressive phases appear later in life, they follow the same seasonal pattern. Oscillations of short duration can be spontaneous or reactive. The latter are intense, sustained emotional reactions, often disproportionate to their cause. The cyclothymic nature of these reactions is shown by the presence of many other spontaneous oscillations.

### Hyperthymic Temperament

People with a hyperthymic temperament were those who were full of drive, hyperactive, lively, optimistic, cheerful, and expansive. In most cases hyperactivity was associated with cheerfulness, optimism, and expansiveness. In some cases not all these features were always present; in such cases we put the emphasis on drive and activity, and classified them as hyperthymic even if the other features were absent.

### Normothymic Temperament

People with a normothymic temperament were those who had average activity within their social setting and whose mood was unremarkable.

### Dysthymic Temperament

People with a dysthymic temperament were those who had limited drive and activity and who were pessimistic and withdrawn. Most of them were also anxious, insecure, overscrupulous, and indecisive.

In a few cases apprehensiveness and easily brought on anxiety were combined with striking hyperactivity; we classified these as hyperthymics.

We diagnosed as suffering from cyclothymia those cyclothymics who came under our care because their mood variations troubled their lives. They correspond to the cyclothymic temperamental disorder described by Akiskal.<sup>18</sup>

Of our 118 rapid cyclers, 52 (44%) (15 men and 37 women) had a cyclothymic premorbid temperament. Another 52 (15 men and 37 women) had a hyperthymic temperament. Six patients (5%), (1 man and 5 women) had a dysthymic temperament, and 8 (7%) (5 men and 3 women) were normothymic.

We examined separately the premorbid temperaments of those who were rapid cyclers from the beginning and of those who became rapid cyclers later. We found that the former had a much higher percentage (66%) of premorbid cyclothymic temperament and a lower percentage (28%) of premorbid hyperthymic temperament than patients who became rapid cyclers later (36% cyclothymics and 50% hyperthymics). This probably shows that cyclothymic temperaments have a greater tendency to become spontaneous rapid cyclers when their mood oscillations become pathologic than the hyperthymic temperaments, upon which the action of antidepressants is needed more in order for them to become rapid cyclers. The substantial number (36%) of rapid cyclers with premorbid cyclothymic temperament and a different previous course

shows, however, that many cyclothymics also need the action of antidepressants to become rapid cyclers.

#### CLINICAL PROBLEMS

The possibility that in some manic-depressive patients antidepressants can worsen the further course of the disease raises the questions of how they should be treated and how antidepressants should be administered. Above all, these questions concern patients with a premorbid cyclothymic or hyperthymic temperament and patients who have had a postdepression hypomania. Concern about the future course of the disease of these patients should prevail over the need of immediate clinical success. In this respect, the ideal treatment should be to allow the depression to end spontaneously; anxiolytics and sleeping medication may be given. In fact, when the depression is neither severe nor dangerous, it is possible to let it finish by itself. Of course, most patients who seek psychiatric help need prompt treatment. Risk of suicide, severe sufferings, and the possibility of a long-lasting depression make treatment necessary. ECT is certainly a good alternative to antidepressant drugs, but many patients refuse it, many psychiatrists do not use it or do so reluctantly, and in some places it is practically prohibited. It must be clearly stated, however, that ECT is not only far more effective than antidepressant drugs, but the free intervals following it are much longer. The data of Hoheisel,<sup>10</sup> Bratfos and Haug,<sup>19</sup> Till and Vučković,<sup>11</sup> and this paper confirm this.

Nevertheless, in many cases the only choice is antidepressant drugs. In these cases, and when there is the danger of an acceleration of the course, antidepressants should be used with caution. Unnecessarily high doses should be avoided, because the higher the doses are, the greater is the possibility of postdepression hypomania. The combination of antidepressant drugs with ECT is sometimes used. We have observed that this combination provokes more hypomanias than do these treatments given separately.

Probably different antidepressants have different capacities to provoke mania or hypomania. We have no data to support this, but our clinical impression agrees with van Scheyen and van Kammen,<sup>20</sup> who found clomipramine more active than amitriptyline in inducing postdepression mania.

It is most important to lower the antidepressant dosage when the depression improves and to stop it as early as possible. The widespread practice of consolidating the recovery by continuing antidepressants for weeks or months beyond the end of the depression should be avoided. They can activate, intensify, and maintain hypomanias, but eventually a new depression will follow.

In the present state of antidepressant therapy, lithium is of decisive importance in preventing the acceleration of the course of the disease. In previous papers,<sup>21-23</sup> we discussed the poor response to lithium of patients with a course of depression-hypomania-free interval and of patients with a rapid cycling course, as well as the therapeutic procedure to follow in these cases. We emphasize the importance of the prevention of the postdepression hypomania, but this is difficult as long as the depression ends under the action of antidepressants, and especially when they cause a switch from depression to hypomania. The advisable procedure is to achieve an early suppression of the

hypomania by stopping antidepressants and increasing the lithium dose. This will attenuate the following depression. Maintenance of this procedure, over a number of episodes if necessary, will attenuate and shorten the depression to a point where it will be possible to let it finish spontaneously and allow lithium to exert its full prophylactic effect.

#### HOW FREQUENT IS THE RAPID CYCLING COURSE TODAY?

To determine how many patients with recurrent affective disorders have a rapid cycling course, we examined our records of the last 3 yr. To avoid accumulation of special cases from past years, we included in our material only those patients who came under our care for the first time during the last 3 yr either as outpatients at the Centro Lucio Bini in Rome or as inpatients at the Belvedere Montello hospital.

We used the criterion of at least two distinct affective episodes. Those with at least two depressions we classified as unipolar. We classified those with at least one depression and one mania as BPI. Those with at least one depression and one hypomania were classified as BPII. The patients who at the time of the first consultation had a course of at least four affective episodes per year were classified as rapid cyclers.

Patients with distinct past episodes but who at the time of the first consultation suffered from depression that had lasted more than 2 yr were classified as chronic depression. We classified as cyclothymia the condition of alternating affective disorders of depressive and excitatory type, none of which, however, reached the prolonged severity of affective episodes. We excluded first depressions to make sure that all the patients selected suffered from recurrent affective disorders.

Of a total of 501 manic-depressive patients, 151 (30%) were unipolar depressives, 105 (21%) were BPI, 103 (20.5%) were BPII, 47 (9%) suffered from chronic depression, 15 (3.5%) suffered from cyclothymia, and 80 (16%) were rapid cyclers.

It is important to note the high percentage of patients with rapid cycling course. By using the criterion of the first outpatient consultation with us or the first hospitalization at our facility, we have avoided some bias in selection. Yet we think that this percentage is substantially higher than what could be found in a truly unselected population of affective patients. The overestimation of rapid cyclers among our patients is due to the frequent changes of their physicians by these patients in an attempt to find a remedy for their frequent recurrences. We believe, however, that our percentages approximate the kind of affective population that psychiatrists have to deal with today.

Our finding of 16% of rapid cyclers among manic-depressive patients is much higher than any finding in the older literature. This finding further supports the results of this paper, which show that the use of antidepressant drug treatments increases the frequency of recurrences in many patients.

#### DISCUSSION

Doubts could arise about the causal connection between the transformation of the course of the disease and the antidepressant treatments, but this connection becomes clear when the antidepressants are suspended during a

rapid cyclic course: the phases become as long as they were in the previous course. In a smaller number of cases rapid cyclicity continues beyond the suspension of antidepressants. The cause of this difference is unclear.

It is obvious that not all depressions treated with antidepressant drugs undergo an acceleration of their course. Our material shows that those patients who tend to develop a hypomania after depression are the most likely to undergo an acceleration under the action of antidepressants. Patients with a hyperthymic or cyclothymic temperament clearly have this tendency. We think that these highly energetic persons have times of latent hypomania, which is intensified by antidepressants. The same is true for mild hypomanias of the cyclothymic temperament. Akiskal<sup>18</sup> found that 11 of 25 cyclothymic patients who were treated with tricyclics experienced hypomania. We believe that this intensification of hypomanic processes will, in turn, accentuate the depressive oscillation that follows, which otherwise would have passed unperceived or would not have taken place at all. We derive this hypothesis from the clinical fact that most manias are followed by a depression. At this point the question should arise as to why an intensified hypomania precipitates the following depression in advance. As little is known about the underlying chemical processes, this question cannot be answered. It is conceivable, however, that the energetic processes that sustain a mild hypomania or the free interval of a very active person are depleted more rapidly when they are intensified, and the free interval ends more quickly.

The observation that rapidly alternating episodes may follow the first appearance of hypomania under the action of antidepressants was first made by Arnold and Kryspin-Exner.<sup>9</sup> They called this change of the course *Labilisierung*, which means destabilization of the affective functional level. They considered it a form of chronification. Till and Vučković<sup>11</sup> state that of the 60 patients who showed an increase of frequency of recurrences during antidepressant treatment, 11 underwent this *Labilisierung*.

The fact, however, that many rapid cyclers had a premorbid cyclothymic temperament shows that a pattern of short, alternating affective oscillations already existed in many of these patients and antidepressants only activated it. For the other patients the shortening of the depression and the activation of the following hypomania through antidepressants are the changes that lead to rapid cyclicity.

It certainly seems paradoxical that a treatment that is therapeutic for depression can worsen the further course of the disease through the same therapeutic action. But if we consider more carefully the effects of these treatments on the disease, we can conclude that this therapeutic action is a very peculiar one. We shall mention two clinical facts: First, a depression is sometimes spontaneously followed by a mania or a hypomania. This evolution is not prevented by the antidepressant treatment, and, as a matter of fact, is accentuated by it. Second, in continuous circular cases the mania (or hypomania) alternates with depression without a real free interval between them. A few weeks of well-being often separates the two phases as a transition from one to the other. A successful antidepressant treatment shortens the depressive phase, but no free interval follows. The opposite phase is just

anticipated and starts immediately after the depression. This is a unique example in medicine, in which a therapeutic effect does not prevent but rather favors the subsequent evolution of the disease. This peculiar effect must mainly depend upon the peculiarity of what we call manic-depressive disease, but it certainly also depends upon the peculiarity of antidepressants, which seem to accelerate the underlying chemical processes rather than act against them.

Helmchen<sup>24</sup> points to "the probability that the regions and/or means of influence of antidepressant prophylaxis are different from those of antidepressant therapy." It is meaningful that the only proved prophylactic drug against depression is lithium, and the only certain therapeutic action of lithium is its antimanic one. On the contrary, antidepressants intensify the manic process and, by doing so, favor the onset of new depressions.

Depressions seem to have increased in our time. A fundamental question is whether this increase is due to a greater number of people who suffer from depression or to an increased number of recurrences of each depressed patient. Our observations indicate that the number of recurrences has increased in a certain number of patients and that antidepressant drugs may well be the cause.

Our conclusions must be taken as tentative because of the limitations of the method of our investigation. The importance of this subject certainly requires further research.

#### REFERENCES

1. Ritti A.: *Traité Clinique de la Folie à Double Forme*. Paris, Octave Doin, 1883
2. Kraepelin E.: *Psychiatrie* (7 Auflage), Band II. Leipzig, Barth, 1904, p 570
3. Lange J.: Die endogenen und reaktiven Gemütskrankheiten und die manisch-depressive Konstitution, in Bimke O (ed): *Handbuch der Geisteskrankheiten*, Band 6, Spezieller Teil II. Berlin, Springer, 1928, p 181
4. Brodwall O.: The course of the manic-depressive psychosis. *Acta Psych Neurol* 22:195–210, 1941
5. Lundquist G.: Prognosis and course in manic-depressive psychoses. *Acta Psych Neurol, Suppl* 35:1–96, 1945
6. Stenstedt A: A study in manic-depressive psychosis. *Acta Psychiatr Scand* 79:1–111, 1952
7. Freyhan FA: Zur modernen psychiatrischen Behandlung der Depressionen. *Nervenarzt* 31:112–118, 1960
8. Lauber H: Studie zur Frage der Krankheitsdauer unter Behandlung mit Psychopharmaka. *Nervenarzt* 35:488–491, 1964
9. Arnold OH, Kryspin-Exner K: Zur Frage der Beeinflussung des Verlaufes des manisch-depressiven Krankheitsgeschehens durch Antidepressiva. Wiener Medizinische Wochenschrift 45/46: 929–934, 1965
10. Hoheisel HP: Zur Frage der Verkürzung von Intervallzeiten psychopharmacologisch behandelter phasischer Psychosen. *Nervenarzt* 37:259–263, 1966
11. Till E, Vučković S: Über den Einfluss der thymoleptischen Behandlung auf den Verlauf endogener Depressionen. *Int Pharmacopsychiatry* 4:210–219, 1970
12. Siris SG, Chertoff HR, Perel JM: Rapid cycling affective disorder during imipramine treatment: A case report. *Am J Psychiatry* 136:341–342, 1979
13. Wehr TA, Goodwin FK: Rapid cycling in manic-depressive patients induced by tricyclic antidepressants. *Arch Gen Psychiatry* 36:555–559, 1979
14. Lerer B, Birmacher B, Ebstein RP, et al: 48-hour depressive cycling induced by antidepressant. *Br J Psychiatry* 137: 183–185, 1980
15. Tondo L, Laddomada P, Serra G, et al: Rapid cyclers and antidepressants. *Int Pharmacopsychiatry* 16:119–123, 1981
16. Dunner DL, Fieve RR: Clinical factors in lithium carbonate prophylaxis failure. *Arch Gen Psychiatry* 30:229–233, 1974
17. Kretschmer E: *Medizinische Psy-*

- chologie (6 Auflage). Leipzig, Thieme, 1941, p 145
18. Akiskal HS, Djenderedjian AH, Rosenthal RH, et al: Cyclothymic disorder: Validating criteria for inclusion in the bipolar affective group. *Am J Psychiatry* 134:1227-1233, 1977
  19. Bratfos O, Haug JO: The course of manic-depressive psychosis: Follow-up investigation of 215 patients. *Acta Psychiatr Scand* 44:89-112, 1968
  20. van Scheyen JD, van Kammen DP: Clomipramine-induced mania in unipolar depression. *Arch Gen Psychiatry* 36: 560-564, 1979
  21. Kukopulos A, Tondo L: Lithium non-responders and their treatment, in Johnson FN (ed): *Handbook of Lithium Therapy*. Lancaster, MTP Press, 1980
  22. Kukopulos A, Reginaldi D, Ladomada, et al: Course of the manic-depressive cycle and changes caused by treatments. *Pharmakopsychiatry* 13: 156-167, 1980
  23. Reginaldi D, Tondo L, Floris G, et al: Poor prophylactic lithium response due to antidepressants. *Int Pharmacopsychiatry* 16:124-128, 1981
  24. Helmchen H: Current trends of research on antidepressive treatment and prophylaxis. *Compr Psychiatry* 20: 201-214, 1979