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Clinical Relevance and Treatment Possibilities of Bipolar Rapid Cycling

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Key Words

Bipolar disorder · Rapid cycling · Lithium · Anticonvulsants · Thyroxine · Calcium antagonists

Abstract

Bipolar rapid cycling (RC) is defined as 4 or more affective episodes within 1 year. It has been postulated that RC is related to a poor response to lithium, to the same extent as mixed episodes or other atypical symptoms of the illness. This article reviews the current status of alternative pharmacological or otherwise supportive therapies of RC. Biological parameters and characteristics of the illness associated with RC like gender prevalence in women, hyperthyroidism, catecholamine-O-methyltransferase allele, the influence of sleep, different subtypes of bipolar disorder and the risk of antidepressant-induced cycling will be discussed in detail.

Introduction

Rapid cycling (RC) as a longitudinal subtype of bipolar disorder is characterized by the presence of 4 or more depressed, hypomanic, mixed or manic episodes within 1 year. Episodes may occur in an arbitrary sequence with or without a free interval.

The term 'rapid cycling' was introduced by Dunner and Fieve [1] in 1974. It was deduced from the results of a prophylaxis study with lithium showing inferior response in those patients who had had at least 4 affective episodes during the preceding year [1]. However, it took 20 years until this definition was adapted by the *Diagnostic and Statistical Manual of Mental Disorders* IV (DSM IV) [2], and RC has not yet become a valid term in the International Classification of Diseases 10 (ICD 10). Clinical reality, however, is the fact that at least 1/5 of bipolar patients experience an RC course at some stage of their illness. RC may be present right from the start of the illness or may develop during its course, often induced by antidepressant treatment [3, 4].

Special subtypes of RC include ultra-RC (URC) with a change of affective deflections within days or weeks and ultra-ultra-RC (or ultradian RC) with continuous mood instability. It has been suggested that mixed episodes are just cycling with highest frequency or 'ultramaximal cycling'.

Characteristics and Risk Factors for RC

Prevalence and Gender

It has been estimated that 13–20% of bipolar patients suffer from RC [4] with a much higher incidence when looking into patients in special settings [5]. For example, 23 out of 54 patients who had been included in our Stan-

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ley Foundation bipolar outpatient clinics in 1999–2000 exhibit RC (42%); 52% of these rapid cyclers are female. This differs slightly from the literature where 70–90% of rapid cyclers are female. Consequently, the female gender has been discussed as a risk factor for RC [5–8]. Searching for an underlying biological factor, at least the theory that RC is bound to the menstrual cycle could not be verified [9].

Circadian Rhythm

Disturbances of the sleep-wake cycle are a general feature in bipolar patients. Feldman-Naim et al. [10] demonstrated in 15 RC patients that a switch from depression into mania or hypomania is more likely to occur during the daytime, whereas the opposite happens preferentially at night. It can be concluded from these data that extended sleep periods may be helpful in manic RC patients whereas increased activity and light therapy are helpful tools in treating depressed rapid cyclers. This is supported by another study [11] where the best predictor for the development of hypomania or mania in 11 RC patients followed over 18 months was the reduced sleep in the night prior to a switch. Consequently, social rhythm therapy as a psychotherapeutic treatment approach focuses on a stable sleep-wake cycle in RC patients [12].

Thyroid

Hypothyroidism has frequently been associated with RC [13–15]. A first report from Cowdry et al. [15] in 1983 demonstrated a hypothyroid metabolism in 12 out of 24 RC patients, in contrast to 19 non-RC patients with no abnormality. An increased concentration of thyroid antibodies has been observed by Kupka et al. [16] in bipolar patients. This finding was true in all bipolar patients and not specially related to RC [16]. However, there are also contradictory reports [7, 17]. Nevertheless, addition of thyroid hormones appears to be successful in selected RC patients [18–20]. This is also supported by a study of Sack et al. [21] demonstrating a dysfunctional hypothalamus-pituitary-thyroid axis. The healthy controls showed a significant circadian variation of the thyroid-stimulating hormone release which could be increased by sleep deprivation. This reactivity of thyroid-stimulating hormone was not observed in patients with RC.

Regarding the aetiology, lithium-induced hypothyroidism cannot be ruled out completely. A retrospective study in 718 patients receiving lithium for at least 15 months demonstrated a prevalence of 10.4% for hypothyroidism [22]. Female patients had a higher risk than male (14 vs. 4.5%), especially during the first 2 years of treatment.

Catecholamines

Recently, a defect of the catecholamine-O-methyltransferase (COMT) has been discussed as an underlying pathophysiology [23–27]. COMT metabolizes dopamine, norepinephrine and epinephrine. A relation between bipolar disorder and catecholamine metabolism has been suggested and may be deduced both from symptoms as increased or decreased energy, and the usefulness of antidepressants for bipolar depression or dopamine antagonists in treating mania. A recent case report on a 48-hour URC patient demonstrated increased concentrations of metanephrine and epinephrine in the urine during manic episodes [28].

Thus, increased or decreased activity of COMT may relate to bipolar symptoms through an increase or decrease in catecholamines. Whereas there is no clear evidence for such a disturbance in bipolar patients in general [23, 25], an association with the low-activity allele of COMT has been observed in RC and URC patients [24, 26].

Antidepressants

A hot topic of scientific discussion is the use of antidepressants in bipolar depression. Antidepressants may induce mania or increase the frequency of RC [7, 29–32]. Tondo et al. [30] reported on 67 patients with bipolar disorder, with 40 patients developing an RC course after long-term treatment with antidepressants. This appears especially true for tricyclic antidepressants. Selective serotonin reuptake inhibitors appear to have at least a lower switch risk [33]. Other substances with a low switch risk are lamotrigine (LTG) and the monoamine oxidase inhibitor moclobemide [34].

However, it is probably a premature conclusion to promote the monotherapy with a mood stabilizer and to abstain from the use of antidepressants in bipolar depression [35]. Equal efficacy of a mood stabilizer compared to an antidepressant in treating depression has not yet been shown convincingly. Aspects as chronification of depression and suicidality need to be considered. Thus, the combination treatment with an antidepressant and a mood stabilizer should be the first-choice treatment [36–38]. This may be effective both in treating depressive symptoms and reducing the suicide and switch risk. However, antidepressants should probably be discontinued earlier in RC patients compared to non-RC patients.

Bipolar II Disorder

It has been suggested that RC is more common in bipolar II than in bipolar I disorder [17, 39]. This is backed up

by data from patients of our Stanley Foundation Bipolar Network outpatient clinics. As of the end of 2000, 30% of our patients with bipolar I and 73% with bipolar II disorder suffered from RC.

Psychopharmacological Treatment Strategies

The history of RC patients is often characterized by a variety of unsuccessful treatment attempts. So far, an unequivocal standard treatment is still missing. The state of the art of pharmacological and other supportive treatment options will be illustrated in the following paragraphs.

Lithium

Lithium is still considered as a first-choice therapy for the acute and maintenance treatments of classical bipolar I disorder [36, 40, 41]. With the occurrence of dysphoric mania, mixed states and especially RC, the response rate of lithium sharply drops [42–47]. Historically, the term 'rapid cycling' was created when Dunner and Fieve [1] analysed clinical factors associated with lithium non-response in maintenance treatment. In this study, 82% of RC patients were lithium non-responders compared to 41% of non-RC patients. Kukopulos et al. [29] surveyed 434 patients both with a classical course of bipolar disorder and with RC. 20% had an RC course with more female than male patients affected. Out of the 87 patients with RC, 16 had bipolar I and 71 bipolar II disorder. In this study, lithium appeared also ineffective in RC.

A study of Baldessarini et al. [39] involved 360 patients with bipolar I and II disorder with a follow-up of an average of 13.3 years; 56 (15.6%) had a history of RC with 41 (71%) fulfilling RC criteria during the previous year. Only 29.4% of all patients had no recurrence during the observation period. 31.7% of non-RC patients compared to only 13.7% of RC patients were lithium responders.

Valproate

During the 1980s, some case reports suggested a beneficial effect of valproate (VPA) in RC patients [48–50]. An open prospective study of Calabrese et al. [51] in 78 patients followed up for an average of 15.8 months supports both an acute and prophylactic efficacy of VPA in RC patients. Whereas the acute antidepressive efficacy of VPA was low, 54% of manic and 94% of mixed patients responded to VPA. Additionally, VPA was effective in preventing new episodes, interestingly also in preventing new depressive episodes in RC patients [51]. The most common side-effect was gastro-intestinal upset. Using special slow-release formulations may be helpful in preventing these side-effects [52].

Subsequent but smaller open monotherapy trials with VPA [53, 54] as well as studies combining VPA with lithium or carbamazepine (CBZ) [55–57] support the impression of the usefulness of VPA in RC. Additionally, VPA may be helpful in URC [28, 58]. However, large confirmative studies are still missing.

Carbamazepine

CBZ appears to be effective in treating acute mania and preventing new episodes of bipolar disorder [59, 60]. Concerning the treatment of RC with CBZ, there is an obvious lack of controlled data. Retrospective analyses of small studies [61, 62] suggested efficacy of CBZ in RC patients. However, the largest retrospective study analysing 215 patients over 2 years gave no evidence of efficacy in RC patients both for CBZ and lithium [63]. This view is supported by a recent double-blind study comparing lithium and CBZ. For 1 year, patients received either lithium or CBZ. Non-responders were re-randomized to the respective drug for another year. Those patients showing no improvement after the second year were then treated with lithium and CBZ for the third year. As a result, 28% of the RC patients responded to lithium, but only 19% had a benefit from CBZ [64].

In conclusion, the studies so far do not support the use of CBZ in RC patients. Furthermore, most RC patients receive combination treatments with several mood-stabilizing drugs. As CBZ induces P450 enzymes and thus increases drug metabolism, the efficacy of co-medication may be reduced [65].

Lamotrigine

LTG has recently become a focus of interest in the treatment of bipolar disorder, especially bipolar depression. Calabrese et al. [66] proved antidepressive efficacy both for LTG 50 mg/day as well as 200 mg/day compared to placebo.

Several case reports on LTG gave hints for efficacy in RC. This is true both for monotherapy with LTG as well as combination treatment [67–75]. Finally, Calabrese et al. [76] supplied evidence for the efficacy of LTG in a large double-blind prospective study: 324 RC patients initially received LTG as an add-on medication; 182 patients were stabilized and randomized to either placebo or LTG maintenance treatment after discontinuation of other psychotropic medication. After 6 months, no significant difference was observed between groups with respect

to the primary outcome parameter 'time to intervention'. However, for the secondary outcome parameter 'time in study' a significant difference was observed in favour of LTG. Patients receiving LTG remained for an average of 6 weeks longer in the study; 41% of the LTG group compared to 26% of the placebo group had no new episode. Comparing RC patients with bipolar I and bipolar II disorder, the latter had more profit. No serious side-effects, especially allergic reactions, were observed.

Thyroid Hormone Augmentation

Already in 1982, the first report came out demonstrating the usefulness of supraphysiological doses of *L*-thyroxine in 5 out of 10 so far refractory RC patients [77]. Besides several case reports, a few open studies on bipolar patients with or without RC back up these findings [19, 20]. In the study of Bauer and Whybrow [19], 11 previously refractory RC patients experienced with thyroxine a reduction of episodes as well as a reduction of the amplitude of mood swings. Four patients had a complete remission. The same group was followed up for an average duration of 2.5 years, and refractory bipolar patients received *L*-thyroxine as an adition to mood stabilizers [20]. In 20 patients, the number of episodes significantly declined; 8 patients had no further episode.

Doses of *L*-thyroxine in these studies ranged from 200 to 500 μg/day, in some cases up to 600 μg/day. The most frequent side-effects were sweating, an increase in tremor, an increased heart rate and transient ankle oedema. No severe cardiac side-effects or marked osteoporosis caused by *L*-thyroxine have been observed in the studies so far [78].

Calcium Antagonists

The hypothesis of a disturbed calcium homoeostasis [79] in affective disorders led to testing calcium antagonists in RC patients. In an open design, 12 RC patients received either lithium or nimodipine or the combination of both [80]. The combination treatment was superior to both monotherapies suggesting a synergistic effect of lithium and nimodipine [81].

Twelve URC patients received nimodipine in a placebo-controlled double-blind study. Five out of 9 patients finishing the study responded to nimodipine [82]. In another study, the same group demonstrated efficacy of nimodipine monotherapy in 10 out of 30 patients refractory so far to other mood stabilizers. In a second step, the addition of CBZ to nimodipine was helpful in 4 out of 14 non-responders [83]. Nimodipine is a generally well-tolerated drug; however, due to its short half-life, it has to be taken 3–4 times a day which may definitely cause compliance problems.

Atypical Antipsychotics

Atypical antipsychotics are increasingly used in the treatment of bipolar disorder [84]. Clozapine was the first atypical antipsychotic tested in affective disorders [85]. It has a unique receptor profile combining 5-HT2- and dopamine D_1–D_5 antagonism. Although mainly used in refractory patients, clozapine appears useful in treating both mania and RC [86–90].

As far as the new generation of atypical antipsychotics is concerned, there is first evidence for a positive effect of risperidone in RC patients. In a 6-month mirror image comparison of 10 RC patients, Vieta et al. [91] showed benefit of risperidone in 8 of 10 RC patients. However, not only for clozapine and risperidone, but for all atypical antipsychotics, large-scale controlled trials are still missing to establish undoubtful efficacy in the treatment of RC.

Psychotherapy

Psychotherapy in bipolar patients in general still needs more scientific evaluation. Especially in RC patients, no controlled data are available. There is one case report showing the advantage of combined cognitive behavioural therapy and pharmacological treatment compared to drug monotherapy [92].

Further Treatment Options

Electroconvulsive Therapy

Electroconvulsive therapy is still the most effective treatment of affective disorders, both for depressive [93] and manic episodes [94, 95]. For RC patients, a case report [96] and an open case series of 20 patients with treatment-refractory affective and schizo-affective disorders [97] gave at least a hint to effectiveness of electroconvulsive therapy in RC.

Magnesium

In a small open case series of 9 refractory RC patients, 4 patients receiving 40 mEq/day magnesium aspartate hydrochloride improved [98]. The rationale behind the study was the chemical similarity between magnesium and lithium. However, subsequent studies following up these findings are still missing.

Choline

Six RC patients were treated with choline in an open design [99]. Choline was well tolerated, and 4 patients showed marked improvement of their affective symptoms. Again, large-scale controlled trials are still missing to back up the efficacy of choline in RC.

Conclusion

RC is a difficult-to-treat condition and may have a disastrous impact on patients. The quality of life is severely impaired due to the frequent episodes and subsequent hospitalizations. In contrast to the severity of this condition, there is a paucity of knowledge on treatment which is backed up by scientific studies. Thus, we still have to rely mainly on open case series and small uncontrolled studies.

Manic Episode within RC

Evidence so far suggests that lithium is less effective in RC than in non-RC bipolar patients. Large case series show that VPA may be more effective. Alternatively, CBZ or atypical antipsychotics should be tried if VPA fails. Additionally, social rhythm therapy leading to sufficient sleep and the avoidance of too much light exposure may be helpful.

Depressive Episodes within RC

Tricyclic antidepressants should be avoided as they may induce mania and increase episode frequency. Selective serotonin reuptake inhibitors are not only better tolerated, but also have a lower risk of inducing a switch. In every case, a mood stabilizer is mandatory as the basic treatment. If depressive episodes are more frequent and severer than manic ones, e.g. in bipolar II disorder, LTG may become a future first-choice treatment. Additionally, addition of supraphysiological doses of *L*-thyroxine should be tried in refractory patients.

Prophylaxis of RC

RC is associated with an inferior response to lithium maintenance treatment. Again, open data suggest a beneficial effect of VPA. The data for CBZ are controversial; some studies suggest superiority compared to lithium, whereas others could not demonstrate any benefit of both treatments. Again, LTG may become a future first-choice treatment especially in bipolar II RC patients, and high dose *L*-thyroxine or nimodipine may additionally stabilize cycling patients.

Although the tendency is clearly towards combination treatment in RC patients, regular checks for candidate drugs to taper off should be performed. As suggested by Wehr and Goodwin [100] and Kukopulos et al. [3], discontinuing antidepressants may already reduce the frequency of episodes.

For the coming years, it can be expected that several new candidates for the treatment of RC will appear on the stage. This includes new atypical antipsychotics, e.g. quetiapine and ziprasidone, as well as new anticonvulsants, e.g. topiramate or retigabine, and innovative treatments like ω-3 fatty acids. Hopefully, more effort will be made to obtain scientific proof for their efficacy in controlled studies in order to come to an evidence-based and optimized treatment of RC.

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