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The use of mifepristone in the treatment of neuropsychiatric disorders

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Mifepristone is a potent glucocorticoid and progesterone receptor antagonist. The pathophysiology of a number of neuropsychiatric disorders implicates abnormalities in glucocorticoid function. These include mood disorders such as psychotic major depression and bipolar depression. In addition, cognitive disorders such as Alzheimer's disease might also be partially mediated by abnormalities in the hypothalamic–pituitary–adrenal axis. Preliminary studies suggest that mifepristone might have a role in the treatment of a number of neuropsychiatric disorders.

Introduction

Mifepristone is a derivative of the progestin northindone, which has a high affinity for the progesterone and glucocorticoid II (GRII) receptors [1]. In addition, mifepristone is a low affinity binder of the androgen receptor. It has little or no effect on estrogen, monoamine, histamine, muscarinic or mineralocorticoid receptors [2]. Its antiprogesterone effects became evident at Roussel Uclaf, where it was synthesized in the early 1980s, and its applications in the medical termination of pregnancy have been responsible for most of the controversy surrounding the drug. The application of the antiprogesterone effects of the drug have led to investigation of mifepristone in the treatment of endometriosis [3], as a contraceptive [4] and in the treatment of progesterone-sensitive tumors such as meningioma, utererine myomas [5] and breast, prostate and ovarian cancer [6].

By contrast, investigations into the application of mifepristone as an antiglucocorticoid agent have lagged behind the more extensive work that has been completed on antiprogesterone effects [7]. Mifepristone has been used successfully in the treatment of Cushing's syndrome secondary to ectopic adrenocorticotropic hormone (ACTH) hypersecretion or adrenal tumors.

Mifepristone appears to have a specific effect on glucocorticoid receptors. Two types of glucocorticoid receptors have been identified: GRI and GRII. GRI also a the mineralocorticoid receptor is a high-affinity receptor for cortisol [8]. GRI has approximately ten times the affinity for circulating cortisol than does GRII. Thus, the GRII receptor will only be occupied when GRI is saturated. Whereas GRI appears to mediate more rapid adaptations of the hypothalamic–pituitary–adrenal (HPA) axis, GRII appears to be more involved in the long-term effects on the stress response.

Mifepristone eliminates the negative feedback control of cortisol on ACTH [9]. Thus, mifepristone results in an increase in both cortisol and ACTH. The antiglucocorticoid effects of mifepristone are dose dependent and can be reversed by glucocorticoids. For example, 1 mg of dexamethasone antagonizes 400 mg of mifepristone [7]. Unlike other antiglucocorticoids, mifepristone appears to spare pituitary and adrenocortical reserves with short-term use [10]. In addition, mifepristone might have mild glucocorticoid agonist activity [11]. The selective antagonist and mild agonist properties of mifepristone in the absence of endogenous or exogenous corticosteroid might explain why even chronic use of the drug has rarely been associated with hypoadrenalism. [12,13]. However, the rate of hypoadrenalism in patients on mifepristone is difficult to assess because mifepristone will raise cortisol and ACTH levels and confound the laboratory assessment of hypoadrenalism. Thus, the diagnosis of adrenal insufficiency in mifepristone treated patients must be made by the evaluation of clinical signs and symptoms rather than by measuring cortisol levels.

Rationale for use of a glucocorticoid receptor antagonist in psychiatry

A number of neuropsychiatric disorders have been characterized by abnormalities in the HPA axis, including major depression and its subtypes, anxiety disorders such as post-traumatic stress disorder and panic disorder, and cognitive disorders such as Alzheimer's disease and minimal cognitive impairment of aging [14].

The HPA abnormalities in major depression have been studied more extensively than have any other psychiatric disorders. Major depression is associated with elevated levels of urinary free cortisol and, in plasma, 24-hour 17-hydroxycorticoid, basal cortisol and corticotropin-releasing factor (CRF), and nonsuppression in the dexamethasone suppression test (DST) [15]. Psychotic major depression has been particularly associated with HPA abnormalities [16].

Cortisol hypersecretion and resistance to dexamethasone suppression might be an artifact of chronic stress states, including depression. Alternatively, abnormalities

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in the HPA axis might directly contribute to symptoms of neuropsychiatric disorders.

At least two lines of evidence suggest that HPA overactivity might lead directly to the symptoms of some disorders. One piece of evidence is that exogenous glucocorticoids are frequently associated with psychiatric symptoms. Glucocorticoids, such as cortisol and prednisone, particularly when given at high doses for extended periods of time, might produce symptoms that include depression, hypomania, insomnia, cognitive deficits and psychosis [17]. Another source of evidence that HPA abnormalities are involved directly in the pathophysiology of some neuropsychiatric disorders comes from patients with Cushing's syndrome. This condition is frequently associated with mood and cognitive symptoms, and in some cases with suicidality and psychosis [18]. There appears to be a direct correlation between the severity of symptoms and circulating cortisol levels [19]. As the cortisol levels normalize with treatment, neuropsychiatric symptoms tend to resolve [20]. Thus, both exogenous and endogenous hypercortisolemia might produce, and not just be a consequence of, neuropsychiatric symptoms.

DST nonsuppression has been associated with specific symptoms, including cognitive deficits, mood lability, anxiety and decreased libido. In one study, Reus [21] found that nonsuppressors in the DST tended to be more anxious and have more suicidal thoughts as well as insomnia, regardless of their primary diagnosis.

If hypercortisolemia is involved directly in the pathophysiology of neuropsychiatric disorders, then antiglucocorticoid agents would be expected to have a role in the treatment of these disorders. Several types of anticortisol agent have been investigated in psychiatric disorders. These include cortisol synthesis inhibitors such as ketoconazole, CRF antagonists and glucocorticoid receptor antagonists such as mifepristone.

A number of small, open-label and double-blind studies have examined the use of cortisol synthesis inhibitors in the treatment of depression. For example, in a double-blind study of 20 depressed patients, ketoconazole was associated with significant antidepressant effects only in those patients who were hypercortisolemic at baseline [22]. A number of open-label studies also support an antidepressant effect of ketoconazole, metyrapone and aminoglutethimide in unipolar and bipolar depression [23]. In addition, there is a suggestion that ketoconazole might relieve depressive but not psychotic symptoms in patients with schizophrenia and schizoaffective disorder [24]. The available literature on cortisol synthesis inhibitors in the treatment of depression includes fewer than 120 patients [25]. Although the majority of studies have suggested that cortisol synthesis inhibitors have antidepressant benefits, limited conclusions can be drawn, given the small sample sizes and primarily open-label design of these studies. In addition, cortisol synthesis inhibitors such as ketoconazole might also have significant side effects at doses that suppress cortisol synthesis (usually greater than 400 mg/day). These include decreased androgen and aldosterone synthesis, elevations in pregnenolone, nausea, vomiting and, more rarely, hypoadrenalism and hepatotoxicity [26].

A second anticortisol strategy involves the use of CRF antagonists. Central administration of CRF in laboratory animals produces symptoms akin to depression, including sleep disruption, a reduction in exploratory behaviors, increased nervousness, decreased appetite, psychomotor slowing and decreased libido [27,28]. A number of studies suggest that CRF is hypersecreted in depression [29,30]. In animal models of depression, CRF antagonists appear to have antidepressant and anxiolytic properties [31]. However, only one human open-label Phase II study has been completed to date. In a 30-day study, 20 patients received two different dosing regimens of the CRF antagonist R121919 [32]. The patients experienced significant improvements in depression and anxiety at the day 30 endpoint. In addition, affective symptoms worsened when the drug was withdrawn.

Mifepristone in the treatment of neuropsychiatric disorders

Mifepristone might have advantages over other cortisol-specific strategies in the treatment of psychiatric disorders. It appears to be well tolerated and has not been associated with adrenal insufficiency or hepatotoxicity. It has been extensively studied since the early 1980s and much is known about the safety profile of mifepristone.

Evidence that mifepristone might have psychotropic effects emerged in a study by Van der Lely *et al*. [33]. Two patients with advanced Cushing's syndrome who developed severe depression, suicidality and psychoses had substantial resolution of these symptoms within 48 hours after the administration of mifepristone.

Mifepristone has been investigated primarily in the treatment of depressive disorders (Table 1). Murphy *et al.* [34] completed an open-label study of mifepristone 200 mg/day in four nonpsychotic patients with chronic depression. Patients were treated for up to eight weeks, and three of the four were said to have improved. However, only one patient completed the full eight weeks, and this patient did not achieve substantial benefit. The other patients discontinued between two and six weeks as a result of side effects, which might not have been related to mifepristone, including diarrhea and worsened hip pain. Because psychotic depression might be characterized by more consistent HPA dysregulation than is the case for other types of depression, Belanoff *et al.* [35] examined the psychotropic effects of mifepristone in a group of five patients with psychotic depression. In a double-blind, crossover design, patients were treated for four days with mifepristone 600 mg/day or placebo and then crossed over to the alternate treatment. All five patients showed a substantial improvement in depression, and four of five also experienced an improvement in psychotic symptoms. An open-label study examined the dose-related effects of mifepristone in psychotic depression [36]. Thirty patients were randomized to seven days of open-label treatment with 50 mg/day, 600 mg/day or 1200 mg/day mifepristone. The low dose, 50 mg/day, is thought to have significant antiprogesterone effects but no substantial effects on cortisol. Of the 19 patients treated in the 600–1200 mg group, 13 had at least a 30% decrease in psychotic symptoms, as measured by

Table 1. Mifepristone in the treatment of neuropsychiatric disorders

Psychiatric disorder	Study design	*n*	Dose	Duration	Outcome	Refs
Depression	Open label	4	200 mg/day	8 weeks	3 out of 4 improved	[34]
Psychotic depression	Double blind crossover	5	600 mg/day	4 days	5out of 5 improvement in depression 4out of 5 improvement in psychosis	[35]
Psychotic depression	Open label	30	50 mg/day 600 mg/day 1200 mg/day	7 days	13 out of 19 in 600–1200 mg/day group improved 4 out of 11 in 50 mg/day group improved	[36]
Psychotic depression	Double blind parallel group	208	600 mg/day	7 days dosing + usual treatment with 28-day follow-up	No significant difference between treatment groups	[38]
Psychotic depression	Double blind parallel group	221	600 mg/day	7 days dosing mifepristone versus placebo with up to 56-day follow-up	Improvement in psychosis in mifepristone group > improvement in placebo group at day 7, sustained to day 28	[39]
Psychotic depression	Open label	20	600 mg/day	6 days of dosing with 8 week follow-up	Improvement in psychosis and depression at week 4	[37]
Psychotic depression	Double blind	30	600 mg/day	8 days		
Bipolar depression	Double blind crossover	20	600 mg/day	7 days dosing with 6-week follow-up	Improvement in mood and cognition in mifepristone group > placebo group	[41]
Alzheimer's disease	Double blind	9	200 mg/day	6 weeks	Mifepristone > placebo in Alzheimer's disease assessment scale cognitive subtest	[42]
Schizophrenia	Double blind crossover	20	600 mg/day	7 days	Mifepristone = placebo	[44]

the Brief Psychiatric Rating Scale (BPRS) versus 4 out of 11 patients in the 50 mg/day group. Similarly, 8 out of 19 patients in the high-dose group had a more than 50% improvement in depression, versus only 2 out of 11 patients in the low-dose group. Patients in the high-dose group also experienced the expected rise in cortisol and ACTH levels, whereas the 50 mg/day group did not. More recently, another open-label study found that mifepristone-treated patients with psychotic depression showed significant benefits in both depression and psychosis after six days of treatment [37].

Two larger double-blind placebo-controlled trials have now been completed on mifepristone in the treatment of psychotic depression. In the first study of 208 psychotically depressed patients, the effect of adding seven days of mifepristone or placebo to usual treatment was examined in patients hospitalized for the purposes of the study [38]. Patients admitted to the study were taking an average of four psychotropic drugs. Both treatment groups improved significantly from baseline but did not differ from each other on the primary endpoint (a 30% reduction in the BPRS at seven and 28 days). However, in *post hoc* analyses, patients who received mifepristone were more likely to achieve a complete response (i.e. becoming largely asymptomatic on the Hamilton depression scale [HamD] and the BPRS [HamD < 7, BPRS < 25]). In addition, mifepristone-treated patients were less likely to require antipsychotic drugs and were more likely to be discharged earlier from the hospital. The use of treatments known to be effective (concurrent antidepressant or antipsychotic use and hospitalization) might have reduced the ability to demonstrate a difference between groups on the primary endpoint. In the second study, the use of antidepressant or antipsychotic medication was not allowed for at least seven days prior to randomization or for the duration of the seven days of study drug administration in 221 psychotically depressed patients [39]. Study participants received either placebo or mifepristone 600 mg/day for seven days and were then followed for up to 56 days. Mifepristone-treated patients were significantly more likely to show an improvement in psychotic symptoms by day 7, persisting up to 28 days on the BPRS ($p = 0.041$) and the positive symptom subscale of the BPRS ($p = 0.006$). Significant antipsychotic benefits appeared to persist up to day 56, seven weeks after the study drug was discontinued. Antidepressant effects were not seen at days 7 or 28. However, a trend to improvement on the HamD was seen at day 56 ($p = 0.056$). In both studies, seven days of mifepristone treatment appeared to be well tolerated, with only rash appearing statistically more commonly in mifepristone-treated patient (4%) than in placebo-treated patients. Except for the expected and temporary rise in ACTH and cortisol in mifepristone-treated patients, there were no clinically significant differences between groups on laboratory studies, including blood chemistry, blood counts and electocardiograms. Most recently, Flores *et al.* [40] evaluated 30 psychotically depressed patients randomized to mifepristone 600 mg/day or placebo for eight days. Mifepristone patients were significantly more likely to experience a 50% reduction in psychotic symptoms, as measured by the BPRS, than were placebo-treated patients. Depression also appeared to improve more in the mifepristone-treated patients but this effect did not reach statistical significance.

Mifepristone has also been examined in the treatment of bipolar depression. Young *et al.* [41] investigated the benefits of mifepristone 600 mg/day for seven days versus placebo in 20 patients with bipolar depression. Mifepristone-treated patients experienced significantly greater improvements in cognition (working spatial memory) and mood, as measured by the HamD and Montgomery–Asberg depression scale. In addition, the drug appeared to be well tolerated.

Another possible application of mifepristone is in the treatment of cognitive disorders, including Alzheimer's disease. Pomara *et al.* [42] completed a small double-blind study of mifepristone in patients with mild to moderate Alzheimer's disease. Nine patients were treated with either mifepristone 200 mg/day or placebo for six weeks. Mifepristone-treated patients performed better on the Alzheimer's disease assessment scale cognitive subtest total score by six weeks, with a 2.67-point improvement on active drug versus a 1.67-point worsening in placebo-treated patients. This difference did not achieve statistical significance perhaps because of the small sample size. Although mifepristone appeared to be generally well tolerated, two mifepristone-treated patients developed a rash and one developed a clinically nonsignificant hypokalemia. A more adequately powered double-blind study is currently underway to evaluate the efficacy of mifepristone in the adjunctive treatment of Alzheimer's disease [43].

Given the preliminary data suggesting that mifepristone might improve cognition in patients with Alzheimer's disease and bipolar depression, Gallagher *et al.* [44] examined the effects of mifepristone on cognition and psychosis in schizophrenia. They treated 20 schizophrenic patients with mifepristone 600 mg/day or placebo and then crossed patients over to the alternative treatment. There were no significant differences between groups on measures of cognition or psychosis.

Conclusions

Mifepristone is a drug with a unique pharmacological profile that appears to have potential in the treatment of a number of neuropsychiatric disorders (Table 1). Thus far, the most convincing evidence is that mifepristone appears to produce a rapid reduction in psychotic symptoms in patients with psychotic depression. There is also the suggestion that mifepristone might have some utility in the treatment of other mood disorders and Alzheimer's disease. In addition, many other neuropsychiatric disorders characterized by abnormalities in the HPA axis might also be treated by a potent glucocorticoid receptor antagonist. These include post-traumatic stress disorder, panic disorder, other psychotic disorders, such as schizoaffective disorder, and the minimal cognitive impairment of aging. The favorable side-effect profile of mifepristone relative to cortisol synthesis inhibitors might also provide a low cost-to-benefit ratio if the drug is proven to be effective in the treatment of any of these disorders. Controlled studies, now underway, will help to establish the potential role of mifepristone in the treatment of many neuropsychiatric disorders characterized by abnormalities in the HPA axis.

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