Drugs Ther Perspect (2017) 33:529–534
DOI 10.1007/s40267-017-0444-4

DISEASE MANAGEMENT

Manage psychiatric symptoms in Cushing's syndrome by controlling cortisol levels and usual psychiatric therapy

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Published online: 15 September 2017

Abstract Depression and anxiety disorders are common in Cushing's syndrome (CS); mania and psychosis may also occur. Use screening tools to identify psychiatric symptoms and refer for a proper diagnosis. Symptoms may improve after normalization of cortisol levels, so this is the first step in patients with active CS. Provide patients in remission with usual psychiatric care (i.e. psychological, psychosocial and/or pharmacological therapy) to resolve symptoms and improve health-related quality of life, and continue long-term monitoring.

Excess cortisol linked to psychiatric symptoms

In Cushing's syndrome (CS), long-term exposure to excess cortisol produced by the adrenal cortex may induce brain atrophy and a reduction in hippocampus volume, facilitating the development of psychiatric disorders, particularly in those predisposed by genetic risk [1]. Endocrine conditions in CS are similar to those in chronic stress states and stress-related psychiatric disorders: smaller hippocampal volumes in patients with affective disorders (vs controls) and disturbed regulation of the hypothalamic-pituitary-adrenal axis in patients with depression [1].

Patients with CS commonly have other comorbidities, including cardiovascular complications (e.g. hypertension, atherosclerosis), metabolic disorders (e.g. dyslipidaemia, central obesity, diabetes), thrombotic and bone disorders, and cognitive deficits [1]. Their health-related quality-of-life (HR-QOL) is also affected, especially during active CS, and may remain impaired even after remission of CS [1]. Ongoing psychiatric symptoms contribute to this impaired HR-QOL, despite long-term remission of their CS [1]. Symptoms of anxiety and depression may also be caused in part by patients struggling to adapt to their serious physical symptoms and dysfunction and chronic nature of CS [1].

This article summarizes the management of psychiatric symptoms in patients with CS as reviewed by Santos et al. [1].

Depression and anxiety disorders common in active CS

Depression, the most common psychiatric disorder associated with CS [2], has been reported in 50–80% of patients with active disease [1]. Anxiety disorders, mainly generalized anxiety disorder (GAD) are also reported; however, since anxiety often co-occurs with depression in patients with non-endocrine depression, it is difficult to know whether anxiety occurs independently of depression in patients with CS [2]. GAD occurred in as many as 79% of 20 patients with CS in a cross-sectional study [3], and panic disorder has been reported in 3–37% of patients [1].

Factors associated with depression in the active phase of CS include older age, more severe disease, absence of a pituitary adenoma, female sex, higher pre-treatment cortisol levels and prior adverse life events [1]. No differences in severity of depression have been found between the different aetiologies of CS [4], and it appears that CS

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severity or higher cortisol levels (in active disease) influence psychiatric symptoms more than aetiology [1].

Psychotic disorders and mania less so

In a study of 209 patients with CS, psychotic disorders were present in 8% of patients and were more commonly found in patients with adrenal carcinoma [4]. A wide range in the incidence of mania and hypomania has been reported (3–26.7%) [1]. Other psychiatric symptoms may be reported in patients with active CS (Table 1); these do not necessarily meet the criteria for diagnosis of a psychiatric disorder, but deserve consideration because of their impact on the HR-QOL of patients.

Depression and anxiety disorders less common in remission…

The prevalence of depression and anxiety disorders generally decreases over time after remission of CS [1]. In a longitudinal study of 33 patients with CS [5], 32.1% of patients had major depression 3 months after correction of hypercortisolism compared with12.0% after 6 months and 6.9% after 12 months; anxiety disorders were found in 7.1% of patients 3 months after CS remission, but in none after 6 or 12 months [5]. The prevalence of atypical depression also decreased over time.

…but symptoms may persist

Although psychiatric symptoms improve over time after normalization of cortisol, some patients do not fully recover [1]. Mean depression and anxiety subscale scores on the Hospital Anxiety and Depression scale were higher in 51 patients in CS remission than in 51 matched controls ($p < 0.01$) [6]. Despite CS remission, 20% of patients had possibly clinically-relevant anxiety and 26% depression [6]. Clinicians should be aware of the possibility of persistence of psychiatric symptoms, including subclinical pathology. In addition, new psychiatric diagnoses may be made, even in patients in remission: 3.7% of patients who had never had a prior psychiatric diagnosis were diagnosed after correction of hypercortisolism in one study [5]. Regular monitoring for psychiatric symptoms is, therefore, recommended (Fig.1). Other psychiatric symptoms reported in patients in remission are summarized in Table 1.

Table 1 Psychiatric symptoms other than depression and anxiety in patients with Cushing's syndrome [1]

Active CS	CS in remission
Irritability	Maladaptive personality traits
Emotional lability	Loss of emotional stability
Reduced libido	Hypoactive sexual desire
Insomnia	Insomnia
	Hypersomnia
	Social phobia
	Apathy

CS Cushing's syndrome

Start by assessing psychiatric symptoms

It is important to ask patients with CS directly about the presence of psychiatric symptoms, as patients may not talk spontaneously about such symptoms [1]. For example, the following two specific questions about depression could be asked, as recommended by the UK National Institute for Health and Care Excellence (NICE) clinical guideline on the identification of common mental health problems [7]:

- "During the last month, have you often been bothered by feeling down, depressed or hopeless?"
- "During the last month, have you often been bothered by having little interest or pleasure in doing things?"

Numerous screening tools (mostly self-report questionnaires) are also available to identify, and assess the severity of possible psychiatric symptoms [1].

Follow-up with psychiatric referral if needed

The presence of psychiatric symptoms does not imply a clinical diagnosis and, therefore, proper diagnosis is essential for selecting the appropriate treatment [1]. Responses to these questionnaires can help clinicians to decide whether a formal psychiatric evaluation is necessary (Fig. 1) [1]. A referral to an appropriate healthcare professional competent in performing mental health assessments is required if the clinician is not trained in such assessments [7].

Aim for remission before treating psychiatric symptoms…

As psychopathology often improves after cortisol level normalization [8], the initial approach to managing psychiatric symptoms is to treat the hypercortisolism [9] (Fig. 1). Patients may not respond properly to antidepressant medication until cortisol levels normalize [1], further supporting the recommendation to first aim for cortisol level normalization.

The Endocrine Society Clinical Practice Guidelines (ES-CPG) on the treatment of CS recommend resection of the lesion as the first-line treatment option [10]. In patients

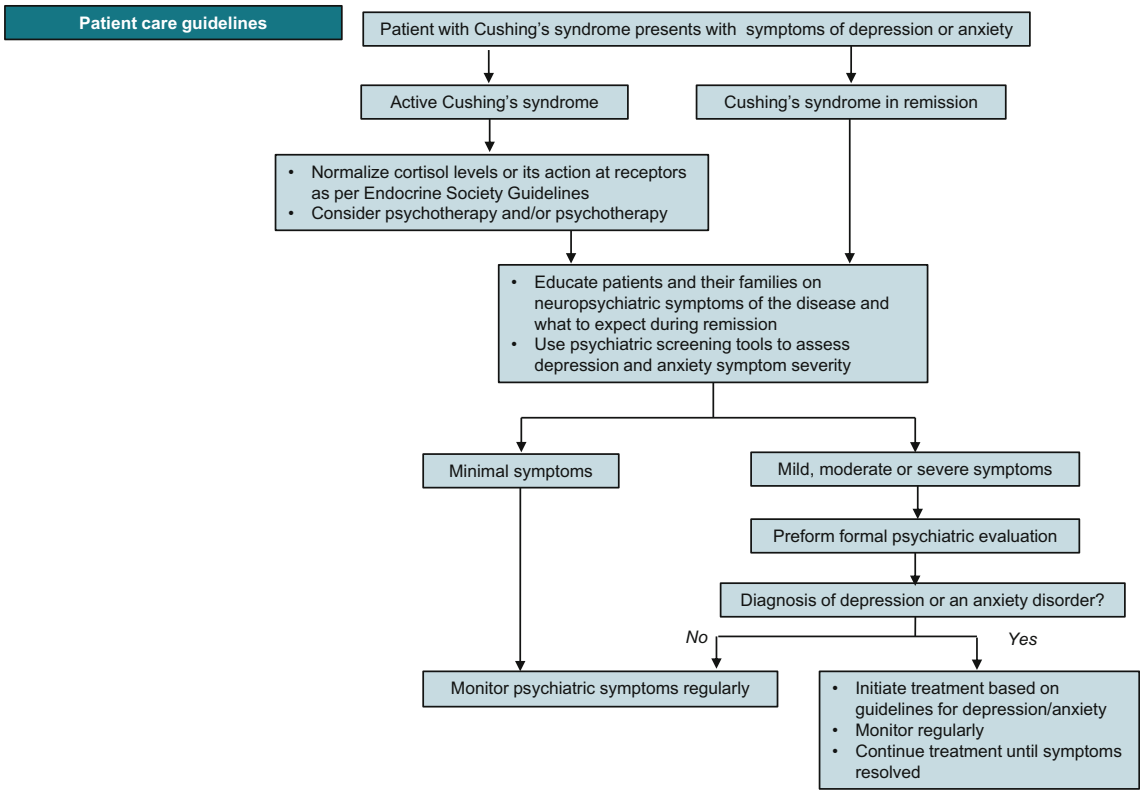

Fig. 1 Management of patients with Cushing's syndrome and symptoms of depression or anxiety, as suggested by Santos et al. [1]

ineligible for surgery or where surgery is ineffective, second-line options include a second surgery (in eligible patients), radiotherapy, pharmacological therapy and bilateral adrenalectomy [10]. In patients with active CS receiving treatment, normalization of cortisol levels may take a long time (at least 6 months) so the clinician should consider recommending psychoeducation and/or psychotherapy in the interim [1].

Significant improvements or even resolution of depression, anxiety, irritability and psychosis have been demonstrated after normalization of cortisol levels in patients receiving pharmacological therapy (i.e. glucocorticoid synthesis inhibitors or glucocorticoid receptor antagonists), radiotherapy or surgery [8]. In patients with more severe CS, glucocorticoid-lowering drugs may be especially useful in improving symptoms of depression [11].

…as some psychiatric medicines may be ineffective

If antidepressant treatment is required in patients with active CS, it has been suggested that selective serotonin reuptake inhibitors (SSRIs) have a partial effect on depression during active CS, while tricyclic antidepressants have very little effect [9]. Low-dose clonazepam has been suggested to treat severe anxiety in patients with CS [2]. However, there is a lack of well-controlled studies of antidepressants and benzodiazepines for psychiatric comorbidities conducted specifically in patients with CS.

Atypical antipsychotics for psychosis?

Psychosis is rare in CS but can be difficult to treat, especially since there may be a lack of response to antipsychotic medication in the active phase of the disease [12]. Although there is a lack of evidence to confirm the efficacy of atypical antipsychotics for psychosis in patients with active CS, they may be considered for treating severe psychotic symptoms or a psychotic depression while accepting the possibility of a lack of efficacy in patients with active CS [1]. According to single case reports, clozapine [13] and aripiprazole + mirtazapine [14] were effective in treating psychosis in patients with active CS. In the latter report, the patient had psychotic depression that stabilized with aripiprazole + mirtazapine while she was hospitalized for adrenalectomy to treat her CS. Her psychosis was resolved 6 weeks after surgery [14].

Consider mifepristone for depression or psychosis…

Mifepristone is recommended by the ES-CPG for treating CS in patients who have persistent disease after surgery,

are not surgical candidates. or have diabetes or glucose intolerance [10]; it is approved for this indication in the US [15]. It may be an option where treatment of psychiatric symptoms is necessary in patients with active CS, especially in those refractory to other CS therapies [1]. Mifepristone significantly improved symptoms of depression in a 6-month, open-label, prospective multicentre study (n = 46), thereby supporting its use in this patient population [16].

Evidence of concomitant rapid improvement in psychosis when mifepristone is used to treat active CS comes from two case reports [17, 18] and a retrospective study of 20 patients, of whom 4 had psychosis [19]. Mifepristone resolved psychotic symptoms in one patient with severe depression and psychosis [17], two patients with acute severe psychosis [18], and three of the four patients with psychosis [19]. Symptoms resolved quickly (within 24 h) in one of these reports [18]. Mifepristone + etomidate also improved psychotic symptoms in a case report of a patient with a ectopic CS, where unspecified antipsychotics had failed to improve the psychosis [20].

…but its long-term safety is unknown

The long-term use of mifepristone is controversial. Adverse events associated with its use are adrenal insufficiency-related adverse events, hypokalaemia and endometrial thickening [1]. Its use is further complicated by having to rely on indirect markers of disease activity for optimising dose and determining clinical efficacy [1, 10]. Close monitoring for hypokalaemia and adrenal insufficiency are required [15].

Usual psychiatric care for patients in CS remission

Psychiatric symptoms in patients in CS remission should be managed in a similar way to those without CS [1]. For example, the NICE guidelines on the management of depression in patients with a chronic physical health problem recommend a stepped-approach to patient management [21]. This approach aims to provide the least costly and least burdensome intervention that will effectively treat the patient [21]. Treatment is 'stepped up' to a more complex intervention only if the initial intervention fails, although any patient presenting with serious needs on immediate contact (e.g. are acutely suicidal) receive the higher-intensity intervention immediately. Treatment options include psychological, psychosocial and/or pharmacological interventions [21].

Psychosocial and psychological therapy for most cases

Psychoeducational programmes, physical activity and group therapy programmes may be effective even for minor affective symptoms [1]. NICE guidelines recommend low-intensity psychosocial interventions for patients with persistent sub-threshold depressive symptoms or mild-to-moderate depression [e.g. structured physical activity programme, group support programme, self-help or computer-based cognitive behavioural therapy (CBT)] [21]. High-intensity psychological interventions, such as group-CBT or individual CBT is recommended for moderate and severe depression or for those patients with inadequate response to initial interventions [21]. Studies of the efficacy of such interventions in patients CS and depressive symptoms are lacking.

In patients with GAD that has not improved after patient education and active monitoring, low-intensity psychological interventions, such as individual non-facilitated self-help and psychoeducation, are recommended by NICE, with CBT being reserved for more severe or refractory cases [22].

SSRIs for depression…

SSRIs are considered the first-line pharmacological option when an antidepressant is required to treat patients in CS remission [1]. NICE guidelines recommend an antidepressant such as an SSRI as an alternative to non-pharmacological options in patients with persistent subthreshold depressive symptoms or mild to moderate depression that did not improve with low-intensity psychosocial therapy, and in combination with individual CBT in patients with severe depression [21].

…and benzodiazepines for anxiety

Short-term benzodiazepines are recommended to treat moderate-to-severe symptoms of anxiety in patients in CS remission; however, clinicians should be aware of the risk of benzodiazepine dependence [1]. NICE guidance on GAD and panic disorder emphasize that pharmacological therapy with benzodiazepines should be only for acute crises [23].

Watch for adrenal insufficiency

The impact of adrenal insufficiency, which often occurs after surgery for CS, on psychiatric symptoms is not well established [1]. The ES-CPG recommend that, after

surgical remission, patients who are hypocortisolemic should receive glucocorticoid replacement and education about adrenal insufficiency [10].

Adopt a holistic approach to patient management…

A multidisciplinary approach to management of the patient with CS and psychiatric comorbidities should be adopted [1]. NICE guidelines emphasize long-term coordination of care across all sectors to ensure an integrated approach to the patient's mental and physical wellbeing [21].

Educate patients and their families

Patients and their families should receive education on CS, and the clinical features of remission, according to the ES-CPG [10], but no specific recommendations are made regarding psychiatric symptoms. NICE guidelines on depression [21] and anxiety [22] include patient education on the nature of these psychiatric symptoms in the first step of patient management.

Patients with CS may find it reassuring to know that, although psychiatric symptoms are common and are related to biochemical alterations, they usually improve over time once the hypercortisolism has been resolved [9]. However, the potential for the improvement to take a long time (at least 6 months), and the possibility that some psychiatric symptoms may persist even after biochemical cure should be included in the education materials [1]. Patient education is likely to help patients feel less afraid and in more control of their disease [1].

Direct patients to support groups

Face-to-face or online support groups may be helpful for dealing with CS [1]. One-fifth of patients have been reported to benefit from participation in a support group [24]. Support groups specific for the patient's psychiatric symptoms could be considered; the NICE anxiety and depression management guidelines both recommend informing patients about support groups [21, 22].

Aim to improve HR-QOL

Patients with CS has persistent impairment in their HR-QOL [25], with psychiatric symptoms and many other comorbidities contributing to low HR-QOL [1]. Successful treatment of hypercortisolism may improve HR-QOL, but normalization of scores may never be obtained, even after many years of control of hypercortisolism [25]. Patient's perceive a significant impact on their life: 71% reported their CS to have affected their lives greatly and 20% reported it affected their life 'a lot' [24].

Being supportive of the patient and listening to their experience of the disease may be very helpful [1]. Maintaining usual activities and returning to work (if possible) will aid recovery from psychosomatic impairment [2], and improvements in self care, new hobbies or challenges, regular exercise, treatment compliance and support from family and friends may help patients improve their HR-QOL [25].

Continue to monitor psychiatric symptoms

In addition to the initial assessment, regular long-term follow up of psychiatric symptoms during both the active and remission phases of CS is recommended [1] (Fig.1), since disease remission does not always result in resolved psychiatric symptoms, and new symptoms may even appear during remission [1]. The ES-CPG recommend monitoring and treatment of psychiatric symptoms until they are resolved [10].

Take home messages

- Psychiatric comorbidities, particularly depression and anxiety disorders, are common in patients with CS and affect patient HR-QOL.
- Symptoms of depression or anxiety often improve after treatment of hypercortisolism, but may persist, or even be reported for the first time, in some patients in CS remission.
- Psychiatric symptoms should be assessed, with expert diagnosis and appropriate treatment with usual psychological and/or pharmacological therapy where necessary.
- Follow-up monitoring for psychiatric symptoms, even after long-term remission of CS, is essential.

Compliance with ethical standards

The article was adapted from *Drugs* 2017;77(8):829–42 by employees of Adis/Springer and was not supported by any external funding.

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