A separate copy of this form must accompany each policy submitted for review. Policies submitted without this form will not be considered for review.

<table>
<thead>
<tr>
<th>Plan: Aetna Better Health</th>
<th>Submission Date: 11/01/2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Policy Number: 0306</td>
<td>Effective Date: Revision Date:</td>
</tr>
<tr>
<td>Policy Name: Dexamethasone Suppression Test for Diagnosing Depression</td>
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</tr>
</tbody>
</table>

Type of Submission – Check all that apply:
- [x] New Policy*
- [ ] Revised Policy
- [ ] Annual Review – No Revisions

*All revisions to the policy must be highlighted using track changes throughout the document. Please provide any clarifying information for the policy below:

**CPB 0306 Dexamethasone Suppression Test for Diagnosing Depression**

Policy is new to Aetna Better Health of Pennsylvania.

Name of Authorized Individual (Please type or print): Dr. Bernard Lewin, M.D.

Signature of Authorized Individual: [Signature]

www.aetnabetterhealth.com/pennsylvania New 11/01/2018
Dexamethasone Suppression Test for Diagnosing Depression

Policy

I. Aetna considers the dexamethasone suppression test (DST) as an aid in diagnosing major depressive disorders experimental and investigational because the test lacks sufficient specificity and sensitivity to be useful.

Aetna considers the use of DST test to help physicians choose medication for members with major depressive illness experimental and investigational because its effectiveness for this indication has not been established.

II. Aetna considers the use of DST test to diagnose or manage borderline personality disorder or post-traumatic stress syndrome experimental and investigational because its effectiveness for these indications has not been established.

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.*
III. Subject to specific case review, Aetna considers the DST medically necessary when it is requested by a psychiatrist as an aid to differentiate psychotic depression from schizophrenia. Studies have indicated that individuals with psychotic depression fail to suppress cortisol after the dexamethasone challenge, whereas those with schizophrenia demonstrate suppression.

See

- CPB 0221 - Quantitative EEG (Brain Mapping)
- CPB 0469 - Transcranial Magnetic Stimulation and Cranial and Electrical Stimulation

Background

Guidelines from the Agency for Healthcare Policy and Research (1993) stated that the descriptive diagnosis of depression is based entirely on the patient's signs, symptoms, and personal history. Only a limited number of basic laboratory tests to detect potential general medical causes for the depression unless specific risk factors, specific positive symptoms on the medical review of systems, unusual symptom profiles, or an atypical course of illness is present, in which case selected additional tests are called for to answer specific diagnostic questions. The guideline stated that the dexamethasone suppression test is not recommended for routine use as a screening tool in primary care outpatients because it lacks sufficient specificity and has lower sensitivity in the less severely ill. However, the dexamethasone suppression test can play a role in differentiating psychotic depression from schizophrenia (AHCPR, 1993).
The consensus paper of the World Federation of Societies of Biological Psychiatry (Mossner et al, 2007) stated that biological markers for depression are of great interest to aid in elucidating the causes of major depression. The authors evaluated currently available biological markers to examine their validity for aiding in the diagnosis of major depression. They specifically focused on neurotrophic factors, serotonergic markers, biochemical markers, immunological markers, neuroimaging, neurophysiological findings, as well as neuropsychological markers. They delineated the most robust biological markers of major depression. These include decreased platelet imipramine binding, decreased 5-HT1A receptor expression, increase of soluble interleukin-2 receptor and interleukin-6 in serum, decreased brain-derived neurotrophic factor in serum, hypocholesterolemia, low blood folate levels, and impaired suppression of the dexamethasone suppression test. However, none of these markers is sufficiently specific to contribute to the diagnosis of major depression.

The dexamethasone suppression test was first developed for diagnosing Cushing Syndrome. The Endocrine Society's clinical practice guideline on the diagnosis of Cushing's syndrome (Nieman et al, 2008) recommended initial use of one test with high diagnostic accuracy (e.g., urine cortisol, late night salivary cortisol, 1 mg over-night or 2 mg 48-hour DST). The guideline recommended that patients with an abnormal result see an endocrinologist and undergo a second test, either one of the above or, in some cases, a serum mid-night cortisol or dexamethasone-corticotrophin releasing hormone (DEX-CRH) test. Patients with concordant abnormal results should undergo testing for the cause of Cushing's syndrome. Patients with concordant normal results should not undergo further evaluation. The guideline recommended additional testing in patients with discordant results, normal responses suspected of cyclic hyper-cortisolism, or initially normal responses who accumulate additional features over time.
Reimondo et al (2008) evaluated if the combined low-dose DEX-CRH (LDDST-CRH) test may have a place in the diagnostic strategy of Cushing’s syndrome. All subjects underwent the same screening protocol including 1 mg DST, 24-hour urinary free cortisol (UFC), and mid-night serum cortisol, followed by the LDDST-CRH test whose results were not used to establish a definitive diagnosis. Plasma dexamethasone concentration was measured 2 hour after the last dose of dexamethasone. Patients qualified for Cushing's syndrome when at least 2 screening tests were positive. A total of 16 patients had Cushing's syndrome; while Cushing's syndrome was excluded in the remaining 15 subjects. Even if not statistically significant, the sensitivity and the negative predictive value of the cortisol 15 minutes after CRH were better than the other tests; on the other hand, the test specificity was lower. All patients classified as indeterminate were correctly diagnosed by the LDDST-CRH test. Nevertheless, the repeated assessment of the screening tests and the active follow-up gave the same correct results. In all of the patients mis-classified by the LDDST-CRH test, the plasma dexamethasone concentrations were in the normal range. The authors concluded that based on the present findings, they suggested that the LDDST-CRH test may still find a place as a rule-out procedure in patients who present with indeterminate results after screening and may be unavailable to repeat testing during follow-up.

Neuroendocrine studies have reported significant changes in hypothalamic-pituitary-adrenal (HPA)-axis regulation in patients with post-traumatic stress disorder (PTSD). Based on baseline assessments and the response to dexamethasone, a hypothalamic over-drive with enhanced glucocorticoid feedback inhibition has been suggested. Moreover, the DEX-CRH test has shown to be a more sensitive test to assess HPA-axis dysregulation in major depression and therefore may provide a useful test tool to probe HPA-axis regulation in PTSD. de Kloet and colleagues (2008) evaluated the effect of PTSD on HPA-axis regulation. These researchers
compared the response to a DEX-CRH test between male veterans with PTSD (n = 26) and male veterans who had been exposed to similar traumatic events during their deployment but without PTSD (n = 23). Patients and controls were matched on age, year, and region of deployment. Additionally, these investigators compared the response of PTSD patients with (n = 13) and without co-morbid major depressive disorder (MDD) (n = 13). No significant differences were observed in adenocorticotropic hormone (ACTH) and cortisol response to the DEX-CRH test between patients and controls. Patients with PTSD and with co-morbid MDD showed a significantly lower ACTH response compared to patients without co-morbid MDD. The response to the DEX-CRH test did not correlate with PTSD or depressive symptoms. The authors concluded that the DEX-CRH test did not reveal HPA-axis abnormalities in PTSD patients as compared to trauma controls. Furthermore, PTSD patients with a co-morbid MDD showed an attenuated ACTH response compared to PTSD patients without co-morbid MDD, suggesting the presence of subgroups with different HPA-axis regulation within the PTSD group.

Muhtz et al (2008) noted that reports about alterations of HPA function in patients with chronic PTSD are inconsistent and controversial. More refined laboratory tests and subgrouping of PTSD patients might help to decrease variance of findings. In a pilot study, these investigators reported the preliminary results of a combined DEX-CRH test in patients with chronic PTSD. A total of 14 subjects with chronic PTSD and 14 healthy controls were examined between 13:00 and 17:00 using a modified combined DEX-CRH test (0.5 mg dexamethasone at 23:00, 100 microg CRH at 15:00). Plasma ACTH, cortisol and blood pressure were measured every 15 minutes from 14:45 until 17:00. No significant differences between patients and controls were found in the analyses of ACTH and cortisol levels, but systolic and diastolic blood pressure were significantly elevated in PTSD. Severity of depressive symptoms had no influence. However, explorative
analyses showed that patients with a history of childhood traumatization had significantly higher post-dexamethasone-ACTH levels and a significantly lower diastolic blood pressure in comparison to patients without early trauma. The authors concluded that in this first pilot study in a typical clinical sample of patients with chronic PTSD, they found effects of severe adverse events in childhood on HPA-axis regulation. Maybe, childhood traumatization could influence HPA-axis findings in PTSD. They stated that further research is needed, especially dose-response studies with different doses of dexamethasone in DEX-CRH tests in patients with PTSD.

Castinetti and colleagues (2009) stated that recurrence of Cushing's disease (CD) after trans-sphenoidal surgery (TSS) occurs in about 25% of cases. Twenty percent of patients with immediate post-surgical corticotroph deficiency will present late recurrence. In a prospective bi-center study, these investigators evaluated a coupled dexamethasone-desmopressin test (CDDT) as a predictor of recurrence of CD. They studied 38 patients treated by TSS for CD with a mean follow-up of 60 months; and evaluated 24-h urinary free cortisol, ACTH, and cortisol plasmatic levels and performed low-dose DST and CDDT 3 to 6 months after surgery and then yearly. After CDDT, ACTH ratio (ACTHr) was defined as (PeakACTH - BaseACTH)/BaseACTH. Cortisol ratio (Cortisollr) was defined as (PeakCortisol - BaseCortisol)/BaseCortisol. Basal values were observed after low-dose DST. Receiver operator characteristics curve defined ACTHr and Cortisollr giving the best sensitivity and specificity associated with recurrence. A total of 10 patients presented recurrence; ACTHr and Cortisollr were superior or equal to 0.5 in all patients with recurrence and in 3 of 28 patients in remission (100% sensitivity, 89% specificity). The test became positive in 8 of 10 patients with recurrence 6 to 60 months before classical markers of hyper-cortisolism. Six patients with immediate post-surgical corticotroph deficiency presented recurrence. All of them presented CDDT positivity during the 3 years after surgery, and recurrence 6 to 60
months after CDDT positivity. The authors concluded that CDDT is an early predictor of recurrence of CD and could be of particular interest in the first 3 years after surgery, by selecting patients at high risk of recurrence despite falsely reassuring classical hormonal markers. The findings of this small study need to be validated by well-designed studies.

Hori et al (2013) stated that evidence showed that depression is associated with HPA axis hyper-activation, although such findings were not entirely unequivocal. In contrast, various psychiatric conditions, including atypical depression, are associated with hypocortisolism. Another line of research has demonstrated that personality is associated with HPA axis alteration. It is thus hypothesized that different personality pathology in depression would be associated with distinct cortisol reactivity. These researchers examined the relationship of temperament and character with cortisol reactivity to the combined DEX-CRH test in depressed patients. A total of 87 outpatients with DSM-IV major depressive disorder were recruited. Personality was assessed by the temperament and character inventory (TCI).

Hypothalamic-pituitary-adrenal axis reactivity was measured by the combined DEX-CRH test. According to the authors’ previous studies, 2 subgroups were considered based on their cortisol responses to the DEX-CRH test: (i) incomplete-suppressors whose cortisol response was exaggerated, and (ii) enhanced-suppressors whose cortisol response was blunted. The analysis of co-variance, controlling for age, gender and symptom severity, revealed that incomplete-suppressors scored significantly higher on cooperativeness than enhanced-suppressors ($p = 0.002$). A multi-variate step-wise logistic regression analysis predicting the cortisol suppression pattern from the 7 TCI dimensions, controlling for age, gender and symptom severity, revealed that lower cooperativeness ($p = 0.001$) and higher reward dependence ($p = 0.018$) were significant predictors toward enhanced suppression. The authors concluded that these findings...
suggested that (personality-related) subtypes of depression might be differentiated based on the different pattern of cortisol reactivity. Moreover, they stated that future studies are needed to further characterize the HPA axis alteration in relation to various subtypes of depression.

An UpToDate review on “Dexamethasone suppression tests” (Lacroix, 2015) does not mention depression, personality disorder, and post-traumatic stress syndrome as indications of dexamethasone suppression test.

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>CPT codes not covered for indications listed in the CPB:</td>
<td></td>
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<tr>
<td>80420</td>
<td>Dexamethasone suppression panel, 48 hours. This panel must include the following: Free cortisol, urine (82530 x 2), cortisol (82533 x 2),and volume measurement for timed collection (81050 x 2)</td>
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<tr>
<td>ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):</td>
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<td>F32.0 - F32.5 F32.9</td>
<td>Major depressive disorder, single episode</td>
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<tr>
<td>F33.0 - F33.42 F33.9</td>
<td>Major depressive disorder, recurrent episode</td>
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<tr>
<td>F43.10 - F43.12 F43.12</td>
<td>Post-traumatic stress disorder</td>
</tr>
<tr>
<td>F60.3</td>
<td>Borderline personality disorder</td>
</tr>
</tbody>
</table>
The above policy is based on the following references:

7. Esel E, Kartalci S, Tutus A, et al. Effects of antidepressant treatment on thyrotropin-releasing hormone stimulation, growth hormone response to L-DOPA, and dexamethasone suppression tests in major depressive patients. Prog

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
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</thead>
<tbody>
<tr>
<td>Z13.89</td>
<td>Encounter for screening for other disorder [depression]</td>
</tr>
</tbody>
</table>


21. Lacroix A. Dexamethasone suppression tests. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed January 2015.
Amendment to
Aetna Clinical Policy Bulletin Number:
0306 Dexamethasone Suppression Test for Diagnosing Depression

There are no amendments for Medicaid.