APPROACH TO ORGANIC CAUSES OF DEPRESSION

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The authors have no conflicts of interest to disclose.

ABSTRACT:

Purpose – To review medical etiologies of depression and suggest a practical investigative approach.

Methods – PubMed, OVID Medline, and Cochrane databases were searched using the key words "organic", "depression" and "diagnosis" in unison and associated MeSH terms for English-language clinical trials, case reports, meta-analyses, reviews conducted with human subjects, and medical textbooks. References from appropriate retrieved articles were also reviewed.

Results – Medical conditions that present with symptoms of depression are often attributed to a diagnosis of major depressive disorder. These patients may be prescribed antidepressants, which will not treat the underlying cause and may cause adverse effects. In these cases, it is important to maintain a broad differential diagnosis and perform a thorough history and physical examination, as well as investigative tests to exclude organic medical conditions that may mimic depression. These organic conditions can often be successfully treated by addressing the underlying disease thereby managing the depressive symptoms.

Conclusion: The most common medical mimickers of depression include endocrine and cardiovascular etiologies, such as hypothyroidism, Addison's disease, anemia and heart failure. A diagnosis of depression and prescribing antidepressants to a patient with symptoms resembling depression should only be done after comprehensive investigations and exclusion of organic medical conditions whose presentation may mimic major depressive disorder.

CLINCAL CASE:

A 31 year old female presented to the Emergency Department (ED) on the advice of a friend in nursing to investigate a large neck mass, growing over the last several months. Associated symptoms included dyspnea, increased stool frequency, weight loss, amenorrhea and weakness for the past year. She had seen her family physician weeks ago complaining of mood lability and difficulties with sleep, and was diagnosed with depression and provided some counseling. On presentation, she denied any other symptoms suggestive of major depressive disorder, but had noticed an unspecified unintentional weight loss and increase in her energy lately. On exam she was restless and unable to lie still. She was afebrile, with sinus tachycardia (HR127 bpm) and hypertension (BP 164/100 mmHg). Examination of her neck identified a diffusely enlarged non-tender thyroid; a thyroid bruit was audible. There was no neck adenopathy (see Figure 1). Additional pertinent findings included moist and warm skin, thinning hair, noticeable tremor, exopthalmos, periorbital edema, lid lag, and proximal muscle weakness. There was no evidence of hyperpigmentation, rash, nail changes or peripheral edema.

INTRODUCTION:

Approximately 12% of Canadians will be diagnosed with clinical depression at some point in their lifetime.[1] In medicine clinics, nonspecific signs and symptoms, such as an outwardly sad appearance, lack of concentration or motivation, irritability, fatigue

and changes in sleep, are often ascribed to major depressive disorder (MDD). A meta-analysis comprising of 50,371 patients across 41 studies reported that for every 100 assessments of MDD seen in primary care, 15 are false positives given a 20% prevalence, resulting in inappropriate initiation of antidepressants theory.[2] Boland found that 40% of all referrals to psychiatry querying depression did not meet criteria for this diagnosis.[3] Berardi and others showed that 25% of primary care patients who were labeled as having MDD without meeting International Classification of diseases (ICD) criteria were started on antidepressants.[4], while the National Comorbidity Survey showed that 40% of surveyed respondents without a diagnosis of depression received treatment for that condition within a 12-month period.[5] This literature suggests that MDD is both over-diagnosed and over-treated.

The DSM-5 explicitly requires differentiation of whether a patient's symptoms are due to a true MDD or the direct physiological effects of a substance or general medical condition in order to correctly treat the underlying diagnosis. A landmark study by Koranyi observed that 43% of patients referred to psychiatry have underlying physical illness, of which nearly 20% have not been diagnosed by their referring physician.[6] Similarly, Hall reported a 9.1% rate of psychiatric symptoms directly attributable to an organic cause .[7] Misdiagnosing depression based on suggestive but vague symptomatology can result in untoward patient consequences including clinical sequelae of the true cause of the symptoms and side effects from the initiation of antidepressants. Treatment with antidepressants for an incorrect diagnosis of depression can be problematic. A review by Bostwick reported that over 10% of adult inpatients who received a psychiatry consultation were started on medication and had an adverse drug reaction sufficiently significant to discontinue the new therapy.[8] Other common antidepressant side effects, including metabolic abnormalities, can worsen the health status of already ill patients.[9] Before a diagnosis of MDD can be made, it is important to consider common mimickers of depression. In cases where clinical suspicion for a non-psychiatric cause of depression is high, appropriate testing should be undertaken to confirm or exclude the medical diagnosis. This paper aims to provide a systems-based approach to rule out depressive symptoms due to general medical conditions.

Clinical Features of Depression
*__M__ood depressed
__S__leep changes (insomnia/hypersomnia)
*__I__nterest lost in activities (anhedonia)
__G__uilt or worthlessness
__E__nergy lack (fatigue)
__C__oncentration diminished
__A__ppetite lost
__P__sychomotor retardation __o__r agitation
__S__uicidal ideation
*must include one of these symptoms
≥5 symptoms for a minimum two-week period

Table 1. Mnemonic for diagnostic symptoms of depression.

Differentiating etiologies of organic depression

A major depressive disorder as defined by the DSM-5 must present with at least five or more of the following symptoms (see Table 1) that qualify a marked change in the individual's previous functioning for a minimum two-week period, and must include depressed mood or loss of interest or pleasure.[10] An important distinction between psychiatric and organic causes of MDD is outlined in a criterion that excludes this diagnosis if the symptoms are secondary to the effects of a medical condition or substance.[10] A history of a temporal association between the onset of depressive symptoms and whether the symptoms are typical or unusual for a primary mood disorder is important. Atypical findings may include the absence of family history, atypical age of onset or the clinical course of the presenting symptoms .[11]

Pharmacologic causes and their associated symptoms are listed in Table 2. While the exact dosages correlated with depressive symptoms can be variable, it is important to consider new onset of the listed symptoms with the addition of any of the listed drugs or a change in the dose of the medication. The non-pharmacologic organic causes, associated symptoms of depression, medical investigations, and pertinent historical and clinical items are shown in Table 3.

Drug class	Associated depressive symptoms
Stimulants* (cocaine, amphetamines) (12)	Depressed mood, anhedonia, insomnia
Alcohol* (12)	
Benzodiazepines* (12)	
Corticosteroids (11)	Insomnia, depressed mood, irritability
Antiretrovirals (13)	Fatigue, concentration issues, decrease in appetite or weight loss
Antiepileptics (14)	Depressed mood
Antipsychotics (11)	
Vincristine, vinblastine (11)	
Interferon (11)	
Indomethacin (11)	
Anti-Parkinson agents (15)	
Methyldopa (11)	
Statins (16)	
Digoxin (16)	
Antihypertensives (propranolol, diltiazem, enalapril) (16)	

Table 2. Common pharmacologic causes of depressive symptoms.
*Withdrawal from these agents may also cause depressive symptoms

	General medical condition	Associated depressive symptoms	Screening investigation	History or physical findings favouring general medical condition
Endocrine	Hypothyroidism	Dysthymia, psychomotor slowing, decreased cognitive functioning (17)	TSH: elevated	Gradual onset, goiter, weight gain, fatigue, cold intolerance, constipation, menorrhagia
	Hyperthyroidism	Irritability, weight loss, sleep changes, dysphoria, concentration impairment (17)	TSH: normal or decreased T4 (free): elevated	Goiter, thyroid bruit, thyroid nodule, restlessness, heat intolerance, hyperdefecation, oligomenorrhea or amenorrhea
	Cushing's disease/ syndrome	Insomnia, depressed mood, irritability (11)	TSH: normal or decreased T4 (free): elevated	Mood swings, headache, polyuria, polydipsia, Cushingoid appearance (cervical & dorsal fat pads, striae, acne, hirsutism)
	Addison's disease	Apathy, poverty of thought, avolition (18)	ACTH stimulation test: positive	Postural dizziness, nausea, vomiting, hyperpigmentation, hypotension
	Hyper-parathyroidism	Fatigue, loss of appetite, depressed mood (19)	Ionized calcium: elevated APTH serum level: elevated	Dysuria, constipation, dehydration, abdominal pain, renal stones
	B12 deficiency	Depressed mood, psychomotor slowing, irritability (20)	B12 serum level: decreased	Paresthesias, symptoms of anemia, posterior column deficiencies (proprioception, tactile sensation)
Cardiac	Congestive heart failure	Insomnia, fatigue (21)	Echocardiogram: low ejection fraction Chest x-ray: pulmonary edema or effusion	Shortness of breath, chest pain, cardiac murmur, edema
	Ischemic heart disease		ECG: signs of old infarct Exercise stress test: impaired	Chest pain, angina, exertional dyspnea, coronary artery disease risk factors
	Anemia		CBC: decreased Hb	Lethargy, fatigue, poor diet, pallor, tachycardia
Neurologic	Alzheimer's disease	Lack of concentration, depressed or irritable mood, psychomotor slowing, weight loss (22)	Cognitive testing (MMSE, Montreal Cognitive Assessment): impaired	Gradual onset, memory loss, personality changes
	Parkinson's disease	Weakness, psychomotor slowing (15, 23)		Tremor, masked facies, rigidity and bradykinesia, loss of balance, shuffling gait, micrographia (24)
	Stroke		CT/MRI brain	Sudden onset, vascular disease, focal neurological deficits
Infectious	HIV/AIDS	Depressed mood, fatigue (11)	Rapid HIV antibody test: positive	High-risk behaviour, lymphadenopathy, HIV wasting
	Neurosyphilis	Unipolar or bipolar depressive symptoms (25)	VDRL: positive CSF analysis: culture positive	High-risk behaviour, chancre, gummata
	Mononucleosis	Fatigue, malaise (26)	Monospot test: positive	Fever, infectious contacts, pharyngitis, adenopathy, splenomegaly
Neoplastic	CNS tumour	Depressed mood, dysthymia, increased irritability and mood lability (27)	CT/MRI brain: mass lesions	Headache, visual changes, focal neurologic deficits
Autoimmune	Rheumatoid arthritis	Chronic pain, fatigue, malaise, decreased appetite and weight loss (28)	Rheumatoid factor: positive ESR/CRP: elevated	Joint swelling, multiple joint involvement, duration >6 weeks (29)
	Systemic lupus erythematosus		Anti-neutrophil antibodies (ANA): positive	Rash (malar or discoid), serositis, arthritis, photosensitivity, oral ulcers (30)

Table 3. Organic causes of depression, with associated clinical findings and suggested investigations.

The most common organic causes of depressive symptoms include endocrine and cardiovascular[6, 7]; diagnosis of these disorders is therefore of the highest yield. Thyroid disorders are also a possible etiology, with hypothyroidism being more prevalent. Clinical features of hypothyroidism include weight gain, fatigue, psychomotor slowing, gradual onset, cold intolerance, constipation and menorrhagia. Examination findings in hypothyroidism include goiter, bradycardia, hypertension, pleural and pericardial effusions, edema, dry hair and skin, macroglossia, and delayed relaxation of deep tendon reflexes. Conversely, a history of weight loss, restlessness and irritability, heat intolerance, hyperdefecation, oligomenorrhea or amenorrhea and increased urinary frequency raise suspicion for hyperthyroidism. Examination findings in hyperthyroidism can include goiter, tachycardia, hypertension, exophthalmos with lid lag, moist skin and fine hair, dyspnea and onycholysis. Mnemonics to aid in remembering some of the common signs and symptoms in hypo- and hyperthyroidism are MOM'S SO TIRED and THYROIDISM respectively (Table 4).

Signs and symptoms of hypothyroidism	Signs and symptoms of hyperthyroidism
Macroglossia	**T**remor
Oedema	**H**eart rate elevated
Menorrhagia	**Y**awn
Slowing (psychomotor, bowels, pulse)	**R**estlessness
Skin and hair dry	**O**ligomenorrhea/amenorrhea
Onset (gradual)	**I**ntolerance to heat
Tired (anemia)	**D**iarrhea
Intolerance to cold	**I**rritability
Raised blood pressure	**S**weating
Effusions	**M**uscle wasting/weight loss
Delayed relaxation of DTR	

Table 4. Mnemonics for common signs and symptoms of hypo- and hyperthyroidism.

With a compatible personal or family history of autoimmune disease, exogenous glucocorticoid exposure and symptoms such as orthostasis, nausea, and skin hyperpigmentation, the threshold for investigating for adrenal insufficiency should be low.[18]

Cardiovascular mimickers of depression are most often caused by anemia, followed by heart failure. Symptoms of anemia include fatigue, malaise, weakness, dyspnea, decreased exercise tolerance, palpitations, headache, dizziness, tinnitus, and syncope. Signs of anemia can include mucus membrane and conjunctiva pallor, tachycardia, orthostatic hypotension and a systolic flow murmur. Although the differential diagnosis for anemia can be extensive, iron-deficiency and anemia of chronic disease are most likely.[31]

Heart failure can be difficult to elucidate as the symptoms can often be vague, such as shortness of breath, fatigue, cough and syncope or pre-syncope. More specific signs can include orthopnea, paroxysmal nocturnal dyspnea, weight gain and edema. Physical findings are typically understood as failures in "forward" (low cardiac output) or "backward" (venous congestion) flow, with signs of the former including hypotension, cool extremities, peripheral cyanosis or a third (S3) heart sound, whereas the latter can manifest as crackles on auscultation, elevated jugular venous pressure with positive abdominojugular reflux and Kussmaul's sign, peripheral edema, and hepatomegaly.

Although the differential of organic causes of depressive symptoms remains broad, other conditions to consider and the clinical features of each of these conditions along with recommended diagnostic tests is provided in Table 3.

CASE REVISITED

In this case, the patient reported new onset sleep and mood disturbance. However, there was no consistent presence of depressed mood or anhedonia for a minimum two week period, thus precluding diagnosis of depression based on the DSM-5 criteria. The history and physical exam was consistent with hyperthyroidism. This was confirmed with labwork demonstrating undetectable TSH level, free thyroxine level of 49 pmol/L (normal 9.0-19.0 pmol/L), free T3 of 47.6 pmol/L (normal 2.76-6.45 pmol/L) and thyrotropin receptor antibody >405 U/L (normal <10 U/L), consistent with a diagnosis of Graves' disease. The patient was started on Metoprolol 50 mg PO BID and discharged home with follow up by endocrinology. An outpatient Tc-99 pertechnetate thyroid scan showed 82% uptake in 24 hours (normal range 8-30%), consistent with Graves' disease. She was started on Methimazole 20 mg PO daily, and was responding well to pharmacotherapy on last follow-up; Methimazole may be started at 10-30 mg PO daily depending on the size of the goiter. Treatment with Thionamides (Methimazole and Propylthiouracil) and Beta-blockers for one to two years can result in a state of permanent remission, with low likelihood of relapse given a normal TSH six months or more after discontinuation of therapy. Other options include Thionamide treatment for three to eight weeks until a euthyroid state is achieved. This can then be follow by ablation with radioiodine as first-line therapy or surgery.

CONCLUSION

Misdiagnosing an underlying medical condition as psychiatric depression may result in inappropriate treatment, adverse effects of antidepressant medication and undermining of the patient-physician rapport. Misdiagnosis can lead to higher morbidity and mortality, especially if treatment is delayed for life-threatening conditions like alcohol or benzodiazepine withdrawal.[32]

In this case, an untreated Graves' disease was masking itself through psychiatric and somatic symptoms shared with MDD. It is important to consider a broad differential diagnosis when patients disclose depressive symptoms to prevent misdiagnosis, and to use clinical correlation in order to evaluate if the underlying medical condition is directly responsible for their presentation.

KEY POINTS

1. Differentiating between depression and depression mimics is important in order to treat the correct underlying cause of a patient's presenting symptoms.
2. A thorough history, physical examination and appropriate investigation can differentiate between a DSM-5 diagnosis of major depressive disorder and a medical condition mimicking depression.
3. The consequences of misdiagnosis include clinical sequelae of the untreated condition and potential adverse effects of antidepressant medications.

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