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Dr. Spiegel: Etiologies of disorders of diminished motivation, and how to differentiate them from depressive disorders

Disorders of diminished motivation: What they are, and how to treat them

These disorders share features of depression, delirium, and catatonia, but key differences have major treatment implications

David R. Spiegel, MD
Endowed Chair and Professor

Alyssa Warren, MD
Resident Physician

Will Takakura, MD
Resident Physician

Lia Servidio, MD
Resident Physician

Nathaniel Leu, MD
Resident Physician

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Department of Psychiatry
and Behavioral Sciences
Eastern Virginia Medical School
Norfolk, Virginia

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Disorders of diminished motivation (DDM)—including apathy, abulia, and akinetic mutism—are characterized by impairment in goal-directed behavior, thought, and emotion.[1] These disorders can be observed clinically as a gross underproduction of speech, movement, and emotional response.

DDM are not classified as disorders within DSM-5, and it remains unclear if they are distinct disorders or symptoms that overlap in other conditions. Some sources support distinct diagnoses, while the traditional position is that DDM are variations along a spectrum, with apathy as the mildest form and akinetic mutism as the most severe form (***Figure, page 12***).[1-3] DDM can result from various neurologic, medical, psychiatric, socioeconomic, and drug-induced pathologies, and may represent differing severity of the same underlying pathology.[1,4] It is postulated that DDM arise from disruptions in the dopaminergic frontal-subcortical-mesolimbic networks.[1,4]

We present 2 cases of patients who developed distinct phenotypes within DDM. Despite differences in presentation and symptom severity, both patients showed clinical improvement on methylphenidate (not the only treatment option) as assessed by the Neuropsychiatric Inventory (NPI),[5] a scale used to measure dementia-related behavioral symptoms that includes an Apathy/Indifference (A/I) subscale.

CASE 1

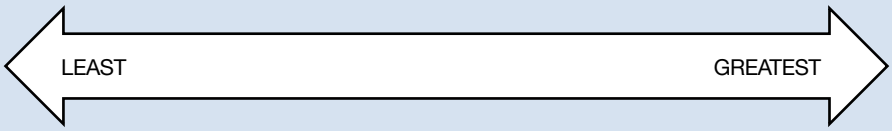
Apathy secondary to glioblastoma multiforme

Ms. E, age 59, presents with wound drainage 3 weeks after a repeat right craniotomy for recurrent glioblastoma multiforme (GBM) of the temporal

Diminished motivation

Figure

Severity of impairment in goal-directed activity in disorders of diminished motivation



Apathy
- Noticeable lack of motivation that varies from baseline
- Reduced goal-directed behaviors or cognition

Abulia
- More apparent decrease in spontaneous, purposeful movement
- Less severe impairment than akinetic mutism

Akinetic mutism

Akinetic = no movement

Mutism = no speech
- Patient is alert with visual tracking intact but *appears* immobilized due to motivational deficit

Source: References 1-3

Clinical Point

It remains unclear if DDM are distinct disorders or symptoms that overlap in other conditions

lobe. Her medical history is not believed to have contributed to her current presentation.

On hospital day 2, Ms. E undergoes debridement and reclosure at the craniotomy site. Prior to the procedure, the patient was noted to have anhedonia and flat affect. Her family reports that she seems to get little enjoyment from life and "only slept and ate." Psychiatry is consulted on hospital day 3 for evaluation and management of a perceived depressed mood.

On initial psychiatric evaluation, Ms. E continues to have a constricted affect with delayed psychomotor processing speed. However, she denies dysphoria or anhedonia. Richmond Agitation-Sedation Scale[6] score is 0 (alert and calm) and test of sustained attention ('Vigilant A') is intact (ie, based on the Confusion Assessment Method for the Intensive Care Unit [CAM-ICU],[7] Ms. E does not have delirium). The NPI A/I frequency score is 15, with a severity score of 3, for a total score of 45, indicating moderate behavioral disturbance on the NPI A/I subsection. A diagnosis of neuropsychiatric apathy due to recurrent GBM or craniotomy is made, although substance-induced mood disorder due to concurrent dexamethasone and opiate use is considered. Methylphenidate, 2.5 mg/d, is started, and Ms. E's blood pressure remains stable with the initial dose.

Methylphenidate is titrated to 5 mg, twice daily, over a 1-week period. Ms. E's NPI A/I subscale score improves to 3 (mild behavioral problem), with 3 points for frequency and a multiplier of 1 for mild severity, reflecting an improvement in neuropsychiatric apathy, and she is transferred to a long-term care rehabilitation center.

CASE 2

Akinetic mutism secondary to subarachnoid hemorrhage

Ms. G, age 47, is brought to an outside hospital with syncope and a severe headache radiating to her neck. Upon arrival, she is unconscious and requires intubation. A non-contrast head CT scan shows diffuse subarachnoid hemorrhage, 6 mm right midline shift, and a small left frontal subdural hematoma. A CT angiography of her head and neck reveals a 0.7 cm anterior paraclinoid left internal carotid artery aneurysm with ophthalmic involvement. Evidence of underlying left and right carotid fibromuscular dysplasia is also seen. Ms. G is transferred to our facility for neurosurgical intervention.

Neurosurgery proceeds with aneurysm coiling, followed by left craniotomy with subdural evacuation and ventriculostomy placement. Her postoperative course is complicated by prolonged nasogastric hyperalimentation, mild hypernatremia and hyperglycemia, tracheostomy, and recurrent central fever. She also develops persistent vasospasm, which

requires balloon angioplasty of the left middle cerebral artery.

The psychiatry team is consulted on postoperative day 29 to assess for delirium. The CAM-ICU is positive for delirium, with nocturnal accentuation of agitation. Ms. G demonstrates paucity of speech and minimal verbal comprehension. She starts oral ziprasidone, 5 mg/d at bedtime. In addition to her original CNS insult, scopolamine patch, 1.5 mg, to decrease respiratory secretions, and IV metronidazole, 500 mg every 8 hours, for skin-site infection, may have been contributing to her delirium.

Ms. G's delirium quickly resolves; however, on day 32 she continues to demonstrate behavioral and cognitive slowing; The NPI A/I frequency score is 28, with a severity score of 3, for a total score of 84, indicating severe behavioral disturbance on the NPI A/I subsection. Methylphenidate, 2.5 mg/d, is started and the next day is increased to 5 mg twice a day to treat severe akinetic mutism. Ms. G also is switched from ziprasidone to olanzapine, 2.5 mg/d at night.

By day 37, the tracheostomy is decannulated, and Ms. G demonstrates a full level of alertness, awareness, and attention. Her affect is full range and appropriate; however, she demonstrates residual language deficits, including dysnomia. On day 38, Ms. G is discharged with an NPI A/I subscale score of 5, indicating a mild behavioral problem.

What these cases demonstrate about DDM

These 2 cases are part of a larger, emerging conversation about the role of dopamine in DDM. Although not fully elucidated, the pathophysiology of abulia, apathy, and akinetic mutism is thought to be related to multiple neurotransmitters—especially dopamine—involved in the cortico-striatal-pallidal-thalamic network.[1,8] This position has been supported by reports of clinical improvement in patients with DDM who are given dopaminergic agonists (***Table 1, page 14***).[3,9-32]

The clinical improvement seen in both of our patients after initiating methylphenidate is consistent with previous reports.[10-13] Methylphenidate was selected because of its favorable adverse effect profile and potentially rapid onset of action in DDM.[10-13] In cases where oral medication cannot be administered, such as in patients with akinetic mutism, short-term adjunctive IM olanzapine may be helpful, although it is not a first-line treatment.[3,15]

Interestingly, both of our patients showed improvement with low doses of methylphenidate. Ms. E showed rapid improvement at 2.5 mg/d, but eventually was increased to 10 mg/d. For Ms. G, who demonstrated severe akinetic mutism, rapid improvement was noted after the initial 2.5 mg/d dose; however, because of reports of efficacy of olanzapine in treating akinetic mutism, it is possible that these medications worked synergistically. The proposed mechanism of action of olanzapine in akinetic mutism is through increased dopamine transmission in the medial prefrontal cortex.[3,15] Ms. G's methylphenidate dose was increased to 5 mg/d, which was still "subtherapeutic," because most reports have used dosages ranging from 10 to 40 mg/d.[10-13] Although there were favorable acute results in both patients, their long-term requirements are unknown because of a lack of follow-up. Our findings are also limited by the fact that both patients were recovering from neurosurgical procedures, which could lead to natural improvement in symptoms over time.

Prevalence of DDM in psychiatric disorders

The successful treatment of DDM with dopaminergic drugs is meaningful because of the coexistence of DDM in various neuropsychiatric conditions. In Alzheimer's disease (AD), disturbances in the dopaminergic system may explain the high comorbidity of apathy, which ranges from 47% in mild AD to 80% in moderate AD.[33] In the dopamine-reduced states of cocaine and amphetamine withdrawal, 67% of patients report apathy and lack of motivation.[8,34] Additionally, the prevalence of apathy is reported at 27% in Parkinson's disease, 43% in mild cognitive impairment, 70% in mixed dementia, 94% in a major depressive episode, and 53% in schizophrenia.[35] In schizophrenia with predominately negative symptoms, *in vivo* and

Clinical Point

The pathophysiology of abulia, apathy, and akinetic mutism is thought to be related to dopamine and other neurotransmitters

Diminished motivation

Clinical Point

Case reports describe abulia and akinetic mutism after cerebral infarction or hemorrhage, although the incidence is unknown

Table 1

Evidenced-based pharmacologic interventions for treating disorders of diminished motivation

Drug	Mechanism of action	Dose	Time of onset/action
Methylphenidate	Blocks dopamine and norepinephrine transporter[9]	10 to 40 mg/d[10-13]	90 minutes to 4 weeks[10-13]
Olanzapine	Increases dopamine and norepinephrine release[14]	2.5 to 7.5 mg/d[3,15]	2 to 8 days[3,15]
Levodopa/benserazide	Dopamine precursor and dopa-decarboxylase inhibitor[17]	50/12.5 to 400/100 mg/d[17,18]	1 day to 1 month[18]
Levodopa/carbidopa	Dopamine precursor and dopa-decarboxylase inhibitor[16]	75/750 mg/d[19]	2 days[19]
Bromocriptine	Dopamine agonist[20]	5 to 150 mg/d[20-23]	1 day to 7 months[20-23]
Donepezil	Cholinesterase inhibitor[24]	5 to 10 mg/d[24]	<24 weeks[24]
Rivastigmine	Cholinesterase inhibitor[25]	4.6 to 9.5 mg/d[25]	<6 months[25]
Modafinil	Alterations of dopaminergic and GABAergic system[26]	100 mg/d[26]	1 month[26]
Bupropion	Dopamine agonist[27]	300 to 600 mg/d[27]	Days to weeks[27]
Pramipexole	Dopamine agonist[28]	0.26 to 2.1 mg/d[28]	3 weeks[28]
Rotigotine	Dopamine agonist[28]	2 mg/d[28]	1 week to 2 months[28]
Ropinirole	Dopamine agonist[28]	2 to 4 mg/d[28]	3 months[28]
Piribedil	Selective D2/D3 dopamine agonist[32]	200 to 300 mg/d[32]	6 weeks[32]

postmortem studies have found reduced dopamine receptors.[8] Meanwhile, the high rate of akinetic mutism in Creutzfeldt-Jakob disease allows for its use as a reliable diagnostic criteria in this disorder.[36]

However, the prevalence of DDM is best documented as it relates to stroke and traumatic brain injury (TBI). For instance, after experiencing a stroke, 20% to 25% of patients suffer from apathy.[37] Many case reports describe abulia and akinetic mutism after cerebral infarction or hemorrhage, although the incidence of these disorders is unknown.[2,38-40] Apathy following TBI is common, especially in younger patients who have sustained a severe injury.[41] One study evaluated the prevalence of apathy after TBI among 83 consecutive patients in a neuropsychiatric clinic. Of the 83 patients, 10.84% had apathy without depression, and an equal number were depressed without apathy; another 60% of patients exhibited both apathy and depression. Younger patients (mean age, 29 years) were more likely to

	Reported duration of treatment	Observed adverse effects
	4 weeks[10-13]	Increased blood pressure,[11] dry cough[13]
	5 to 11 days[3,15]	Akathisia, somnolence[16]
	3 weeks to 5 months[17,18]	Nausea,[17,18] orthostatic hypotension[18]
	Failed to taper[19]	Memory impairment, overeating[19]
	2 days (discontinued due to agitation) to 3 months[20-22] Failed to taper[23]	Agitation and restlessness,[20] dyskinesia[23]
	24 weeks[24]	Nausea, accidental injury, diarrhea, dizziness[24]
	18 months[25]	Asthenia/drowsiness, transient worsening of painful dyskinesia[25]
	8 months[26]	Headache, dizziness, gastrointestinal complaints, sleep disturbances[26]
	4 to 24 months[27]	Seizures[27]
	6 months[28]	Somnolence, dyskinesia, hallucinations, orthostatic hypotension, compulsive behavior[29]
	6 to 12 months[28]	Somnolence, hallucinations, orthostatic hypotension, application site reaction, compulsive behavior[30]
	4 to 12 months[28]	Somnolence, dyskinesia, hallucinations, orthostatic hypotension, compulsive behavior[31]
	12 weeks[32]	Dyskinesia, hallucinations, irritability[32]

be apathetic than older patients, who were more likely to be depressed or depressed and apathetic (mean age, 42 and 38 years, respectively).[41] Interestingly, DDM often are associated with cerebral lesions in distinct and distant anatomical locations that are not clearly connected to the neural circuits of motivational pathways. This phenomenon may be explained by the concept of diaschisis, which states that injury to one part of an interconnected neural network can affect other, separate parts of that network.[2] If this concept is accurate, it may broaden the impact of DDM, especially as it relates to stroke and TBI.

The differential diagnosis of DDM includes depression and hypokinetic delirium (***Table 2***,[1,3,42-50] ***page 16***). A potential overlapping but confounding condition is stuporous catatonia, with symptoms that include psychomotor slowing such as immobility, staring, and stupor.[47] It is important to differentiate these disorders because the treatment for each differs. As previously discussed, there is a clear role for dopamine receptor agonists in the treatment of DDM.

Although major depressive disorder can be treated with medications that increase dopaminergic transmission, selective serotonin reuptake inhibitors (SSRIs) are more commonly used as first-line agents.[44] However, an SSRI would theoretically be contraindicated in DDM, because increased serotonin transmission decreases dopamine release from the midbrain, and therefore an SSRI may not only result in a lack of improvement but may worsen DDM.[48] Finally, although delirium is treated with atypical or conventional antipsychotics vis-a-vis dopamine type 2 receptor antagonism,[45] stuporous catatonia is preferentially treated with gamma-aminobutyric acid-A receptor agonists such as lorazepam.[50]

What to do when your patient's presentation suggests DDM

Assessment of DDM should be structured, with input from the patient and the caregiver, and should incorporate the physician's perspective. A history should be obtained applying recent criteria of apathy. The 3 core domains of apathy—behavior, cognition, and emotion—need to be evaluated. The revised criteria are based on the premise that change in motivation can be measured by examining a patient's responsiveness to internal or external stimuli. Therefore, each of the 3 domains includes 2 symptoms: (1) self-initiated or "internal" behaviors, cognitions, and emotions (initiation symptom), and (2) the patient's responsiveness to "external" stimuli (responsiveness symptom).[51]

continued

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Clinical Point

SSRIs are theoretically contraindicated in DDM because serotonin transmission decreases dopamine release, which may worsen DDM

Diminished motivation

Clinical Point

DDM often are described as a depressive state, even though they lack sadness, desperation, or a depressive mood

Table 2

Key distinguishing features, overlapping characteristics, and treatment differences in DDM

Differential diagnosis	Key distinguishing features	Overlapping characteristics	First-line treatments
DDM	Fully alert and oriented, slowed processing speed, intact vigilance, limited motivation, decreased goal-direction	Anhedonia, psychomotor retardation	Dopamine receptor agonists
Hypokinetic delirium	Inattention, decreased alertness, lethargy, decreased motor activity	Psychomotor retardation	Treatment of underlying etiology
Major depressive disorder	Depressed mood; arousal/awareness intact; lack of prominent language deficits (including confrontation naming); predominately negative feelings or thoughts	Anhedonia, psychomotor, retardation	Antidepressants
Stuporous catatonia	Posturing (maintaining a position for long periods of time); catalepsy (the passive adoption of a posture); negativism (motiveless resistance to instructions); automatic obedience (exaggerated cooperation with the examiner)	Stupor, immobility, mutism	Benzodiazepines

DDM: disorders of diminished motivation

Source: References 1,3,42-50

One of the main diagnostic dilemmas is how to separate DDM from depression. The differentiation is difficult because of substantial overlap in the manifestation of key symptoms, such as a lack of interest, anergia, psychomotor slowing, and fatigue. Caregivers often mistakenly describe DDM as a depressive state, even though a lack of sadness, desperation, crying, and a depressive mood distinguish DDM from depression. Usually, DDM patients lack negative thoughts, emotional distress, sadness, vegetative symptoms, and somatic concerns, which are frequently observed in mood disorders.[51]

Several instruments have been developed for assessing neuropsychiatric symptoms. Some were specifically designed to measure apathy, whereas others were designed to provide a broader neuropsychiatric assessment. The NPI is the most widely used multidimensional instrument for assessing neuropsychiatric functioning in patients with neurocognitive disorders (NCDs). It is a valid, reliable instrument that consists of an interview of the patient's caregiver. It is designed to assess the presence and severity of 10 symptoms, including apathy. The NPI includes both apathy and depression items, which can help clinicians distinguish the 2 conditions. Although beyond the scope of this article, more recent standardized instruments that can assess DDM include the Apathy Inventory, the Dementia Apathy Interview and Rating, and the Structured Clinical Interview for Apathy.[52]

As previously mentioned, researchers have proposed that DDM are simply a continuum of severity of reduced behavior, and akinetic mutism may be the extreme form. The dilemma is how to formally diagnose states of abulia and akinetic mutism, given the lack of diagnostic criteria and paucity of standardized instruments. Thus, distinguishing between abulia and akinetic mutism (and apathy) is more of a quantitative than qualitative exercise. One could hypothesize that higher scores on a standardized scale to measure apathy (ie, NPI) could imply abulia or akinetic mutism, although to the best of our knowledge, no formal "cut-off scores" exist.[53]

Treatment of apathy. The duration of pharmacotherapy to treat apathy is unknown and their usage is off-label. Further studies, including double-blind, randomized controlled trials (RCTs), are needed. Nonetheless, the 2 classes of medications that have the most evidence for treating

apathy/DDM are psychostimulants and acetylcholinesterase inhibitors (AChEIs).

AChEIs are primarily used for treating cognitive symptoms in NCDs, but recent findings indicate that they have beneficial effects on noncognitive symptoms such as apathy. Of all medications used to treat apathy in NCDs, AChEIs have been used to treat the largest number of patients. Of 26 studies, 24 demonstrated improvement in apathy, with 21 demonstrating statistical significance. These studies ranged in duration from 8 weeks to 1 year, and most were open-label.[54]

Five studies (3 RCTs and 2 open-label studies) assessed the efficacy of methylphenidate for treating apathy due to AD. All the studies demonstrated at least some benefit in apathy scores after treatment with methylphenidate. These studies ranged from 5 to 12 weeks in duration. Notably, some patients reported adverse effects, including delusions and irritability.[54]

Although available evidence suggests AChEIs may be the most effective medications for treating apathy in NCDs, methylphenidate has been demonstrated to work faster.[55] Thus, in cases where apathy can significantly affect activities of daily living or instrumental activities of daily living, a quicker response may dictate treatment with methylphenidate. It is imperative to note that safety studies and more large-scale double-blind RCTs are needed to further demonstrate the effectiveness and safety of methylphenidate.

Published in 2007, the American Psychiatric Association (APA) guidelines[56] state that psychostimulants are a possible treatment option for patients with severe apathy. At the same time, clinicians are reminded that these agents—especially at higher doses—can produce various problematic adverse effects, including tachycardia, hypertension, restlessness, dyskinesia, agitation, sleep disturbances, psychosis, confusion, and decreased appetite. The APA guidelines recommend using low initial doses, with slow and careful titration. For example, methylphenidate should be started at 2.5 to 5 mg once in the morning, with daily doses not to exceed 30 to 40 mg. In our clinical experience, doses >20 mg/d have not been necessary.[57]

Treatment of akinetic mutism and abulia. In patients with akinetic mutism and possible abulia, for whom oral medication administration is either impossible or contraindicated (ie, due to the potential risk of aspiration pneumonia), atypical antipsychotics, such as IM olanazapine, have produced a therapeutic response in apathetic patients with NCD. However, extensive use of antipsychotics in NCD is not recommended because this class of medications has been associated with serious adverse effects, including an increased risk of death.[55]

continued

Related Resources

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- Dell'Osso B, Benatti B, Altamura AC, et al. Prevalence of selective serotonin reuptake inhibitor-related apathy in patients with obsessive compulsive disorder. J Clin Psychopharmacol. 2016;36(6):725-726.
- D'Souza G, Kakoullis A, Hegde N, et al. Recognition and management of abulia in the elderly. Prog Neurol Psychiatry. 2010;14(6):24-28.

Drug Brand Names

Bromocriptine • Parlodel
Bupropion • Wellbutrin XL, Zyban
Carbidopa • Lodosyn
Dexamethasone • DexPak, Ozurde
Donepezil • Aricept
Levodopa/benserazide • Prolopa
Levodopa/carbidopa • Pacopa Rytary Sinemet
Lorazepam • Ativan
Methylphenidate • Concerta, Methylin
Metronidazole • Flagyl, Metrogel
Modafinil • Provigil
Olanzapine • Zyprexa
Pramipexole • Mirapex
Rivastigmine • Exelon
Ropinirole • Requip
Rotigotine • Neurpro
Scopolamine • Transderm Scop
Ziprasidone • Geodon

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Clinical Point

Evidence suggests AChEIs may the most effective medications for treating apathy in NCDs, but methylphenidate works faster

Bottom Line

Apathy, abulia, and akinetic mutism have been categorized as disorders of diminished motivation (DDM). They commonly present after a stroke or traumatic brain injury, and should be differentiated from depression, hypokinetic delirium, and stuporous catatonia. DDM can be successfully treated with dopamine agonists.

Diminished motivation

Clinical Point

In patients with akinetic mutism or abulia who cannot take oral medications, consider an IM atypical antipsychotic

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