Mania in the Medically Ill

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Manic symptoms frequently occur in patients with comorbid medical disorders and present a diagnostic and treatment challenge. Manic symptoms may be due to an independent psychiatric illness, may be induced or precipitated by a medical condition, or may result from medication or substance use. The presence of manic symptoms in medically ill patients can lead to misdiagnosis or complicate the management of comorbid medical illness. It is of paramount importance to identify the etiology of the mania and, in particular, differentiate primary from secondary mania. Management of mania in the medically ill should focus on treating the underlying medical condition, medication management (antipsychotic agents, mood stabilizers, and/or benzodiazepines), and psychotherapy (if needed). Selecting appropriate medication for treatment requires basic knowledge of the pharmacokinetics of the medications, their side effect profile, and drug-drug interaction. The majority of deficits accompanying secondary mania resolve with treatment of the underlying cause, and supportive psychopharmacology may be all that is needed, but if symptoms persist, patients may need medications for a longer duration.

Introduction

Mood disorder due to a general medical condition is defined as elevated, expansive, or irritable mood, depressed mood, or markedly diminished interest in or pleasure from almost all activities. It also necessitates evidence from the history, laboratory findings, and physical examination that the mood disturbance is the direct physiologic consequence of a medical condition. Importantly, it cannot be accounted for by another mental disorder and does not occur during the course of delirium. The symptoms cause clinically significant distress or impairment in overall functioning. Type of mood disorder due to a general medical condition can be categorized as with depressive features, with major depressive-like episode, with manic features, or with mixed features. Mania may be accompanied by one or more of the following: excessive involvement in pleasurable activities, increase in goal-directed activity or psychomotor agitation, distractibility, flight of ideas, increased talkativeness, decreased need for sleep, and/or grandiosity [1]. This article will focus on mood disorder due to a general medical condition with manic features. Mania due to a general medical condition often is also termed secondary mania. Thus, primary mania results from bipolar disorder, and secondary mania results from pharmacologic, metabolic, or neurological causes.

Prevalence

The incidence and prevalence of mania due to a general medical condition are unknown. There are different figures reported in regard to prevalence of manic symptoms throughout the literature in various medical illnesses.

Etiologic Factors

Secondary mania has been reported to present with virtually any disorder or process that disrupts brain architecture or physiologic functioning. This includes but is not limited to infection, trauma, tumor, drug withdrawal, drug intoxication, cardiovascular disease, metabolic disturbance, endocrine dysfunction, nutritional deficiency, and demyelinating and neurodegenerative disorders [2]. Please see Table 1 for a list of examples of the causes of disturbances commonly seen. In addition to the disorders, several medications also may have a similar effect on the brain.

Clinical Presentation

The symptoms of mania caused by a general medical condition generally are similar to those seen in primary mania. The clinical presentation of secondary mania can be easily overlapped and confused with delirium. Abrupt onset, inattention, agitation, disordered sleep, and psychosis can be manifestations of each of these disease states. However, the waxing-and-waning course of delirium, along with visual hallucinations and clouding of consciousness should help to differentiate the two diagnoses. Secondary mania should include symptoms of elevated, expansive,

or irritable mood; hypersexuality; grandiosity; flight of ideas; and pressured speech [2].

Primary and secondary mania are often differentiated through the history of time of onset of behavior disturbance and any evidence of organic factors. In secondary mania, the episode usually begins within hours or days of the physiologic or toxic insult. Therefore, a careful psychiatric history screening for symptoms prior to the onset of mania, with collateral information from reliable informants, is crucial to establishing diagnosis. The onset of secondary mania can occur at any time during the lifespan, whereas primary bipolar illness typically has onset during the first 3 decades of life [2]. Therefore, it is especially appropriate to consider secondary mania in an elderly patient who has new-onset mania. According to Shulman et al. [3], the elderly are twice as likely to have a neurological disorder as patients with prior episodes of mania [3]. There also appears to be a bimodal distribution of bipolar illness for women and an increased incidence of mania in old age for men [4]. The mortality rate at 5.6-year follow-up in one study was found to be 50% among elderly manic patients, compared with 20% among elderly people without mania [5]. When cognitive dysfunction or focal neurological signs are present, no personal history or family history of bipolar exists, or if treatment for the affective state is ineffective, then the diagnosis of secondary mania is much more likely. Importantly, approximately 30% of brain-injured patients with mania have at least one relative with unipolar depression [6]. This could mean that the patient is more vulnerable to secondary mania as a result of family history or that the mania is actually primary.

One theory on the underlying mechanism of secondary mania has been postulated in neuroimaging studies by Gafoor and O'Keane [7]. It appears the right frontal lobe or limbic-connecting areas with interruption of the frontotemporal pathways might be involved in the development of secondary mania [7].

Depression, irritability, and anxiety are common symptoms of Huntington's disease [8]. Secondary mania can occur at a rate of approximately 4.8% to 10.0% in Huntington's patients [9,10].

Patients with multiple sclerosis often have multiple frontal lobe disinhibition symptoms, including euphoria and pathological laughing, and it is unknown if this constitutes secondary mania or possibly results in the revealing of primary bipolar disorder [11]. However, standard treatments for mood disorders are beneficial in treatment of affective symptoms in multiple sclerosis. Furthermore, a high level of awareness for suicidal symptoms should be present, as the rate of suicide in patients with multiple sclerosis has been reported at 7.5 times the rate of age-matched populations [12].

In a 1-year follow-up study of 66 patients, Jorge et al. [13] estimated that 3% to 10% of patients with traumatic brain injury would develop manic episodes, and many of them had basal temporal lesions [13]. In most cases, the onset of mania after injury is less than 2 years, although the longest time noted was 12 years [14]. Some researchers have found a preponderance of right-sided lesions related to head injury in patients presenting with manic symptoms [15].

Table 1. Etiologic factors of secondary mood disorders

General medical condition
Infection: meningitis, HIV, syphilis, encephalitis, sepsis, urinary tract infection, pneumonia, influenza
Trauma: subdural hematoma, cerebral contusion
Tumor: systemic or primary cerebral
Cardiovascular disease: infarcts, hemorrhage, vasculitis, congestive heart failure, shock
Metabolic or physiologic disturbance: electrolyte disturbance, renal or hepatic failure, hypo- or hyperglycemia, postictal states
Endocrine dysfunction: thyroid or glucocorticoid disturbance
Nutritional deficiency: vitamin B_{12} or folate deficiency
Demyelinating: multiple sclerosis
Neurodegenerative disorders: Parkinson's disease, Huntington's disease
Neurological disorders: seizures (right temporal), head trauma, stroke, Wilson's disease, multiple sclerosis
Substance-induced mood disorder
Drug withdrawal/intoxication: nicotine, caffeine, alcohol, sedative hypnotics, cocaine, amphetamines, phencyclidine, opiates
Drugs: sedative hypnotics, antipsychotics, antidepressants, metoclopramide, H_2-receptor blockers, antihypertensives, sex steroids, levodopa, bromocriptine, yohimbine, procyclidine, procarbazine, metrizamide, methylphenidate, isoniazid, hydralazine, hallucinogens, disulfiram, cyclosporine, corticosteroids, cimetidine, captopril, bromide, baclofen, amphetamines

The prevalence of mania in HIV-infected patients is estimated to be 4% to 8% [16]. Primary and HIV-related secondary mania are reported to be clinically and immunologically distinct. There has been a correlation noted between secondary mania in HIV-positive individuals and suppressed CD4 counts [17•]. Patients without a family or personal history of mood disorder presented with manic symptoms later in the course of HIV infection and had a higher prevalence of comorbid dementia [18].

Evaluation

Comprehensive evaluation of secondary mania should include detailed history, physical examination, and laboratory and imaging studies, as indicated. Laboratory studies could include blood chemistry, complete blood cell count, liver function test, thyroid function test, erythrocyte sedi-

mentation rate, blood cultures, cortisol levels, HIV test, urine analysis, and urine drug screen. Additional testing may be recommended, if indicated, depending upon the presentation and differential diagnosis. Imaging studies include CT or MRI brain scan, electroencephalogram, x-ray, and lumbar puncture, among any other clinically relevant studies.

Management

The ultimate goal of treatment is rapid control of manic symptoms. Although the acute symptomatic treatment of primary and secondary mania may be similar, appropriate treatment of secondary mania certainly necessitates treating the underlying medical condition. Regardless of the agent used, secondary mania typically does not require prophylaxis like primary mania, unless the mania or hypomanic symptoms in the individual were first recognized during the initial presentation and medical conditions had exacerbated its presentation, or central nervous system (CNS) injury causing manic symptoms continues to persist.

Benzodiazepines and antipsychotics are likely reasonable choices for treatment of acute agitation associated with secondary mania. Shorter-acting benzodiazepines may be more favorable in older individuals, as aging tends to slow the oxidative pathways in the liver; thus, benzodiazepines that are metabolized through conjugated processes, such as lorazepam, are preferred [19••]. Benzodiazepines may be used as adjuvant therapy to decrease agitation and as a short-term treatment for insomnia.

Atypical antipsychotics are preferred over typical antipsychotics because of their more benign side effect profile. Atypical antipsychotics approved by the US Food and Drug Administration (FDA) for the treatment of acute mania include risperidone, quetiapine, olanzapine, aripiprazole, and ziprasidone. Choice of the medication can depend on the underlying medical condition, acuity of presentation, route of administration, side effect profile, and careful evaluation of the drug-drug interaction of the medication of choice with the medications the patient is already taking to treat the medical condition. Newer antipsychotics have faster onset of action than the mood stabilizers and also show good efficacy in controlling symptoms. Fast titration of atypical antipsychotics to effective dosage is crucial for appropriate treatment of the symptoms. Parental administration of antipsychotic agents such as haloperidol alone or in combination with benzodiazepine has been common clinical practice for years to control the agitation and aggression in patients. More recently, a few of the atypical antipsychotics, such as olanzapine, ziprasidone, and aripiprazole, have been approved by the FDA for the treatment of acute agitation associated with underlying psychopathology [20,21].

Paradoxically, several atypical antipsychotics have been associated with mania. Potent blockade of serotonin 5-HT2A but not dopamine D_2-receptors resulting in frontal disinhibition is one of the hypotheses that has been addressed by Richard et al. [22].

FDA-approved mood stabilizers such as lithium, divalproex sodium, and carbamazepine are commonly used in the treatment of manic symptoms. Blood levels of these medications need to be monitored for therapeutic levels. Caution should be used with lithium in hyperthyroidism or unstable fluid/electrolyte disease states. Lithium is contraindicated in systemic lupus erythematosus with renal disease but is effective in the treatment of corticosteroid-induced mania [23]. Divalproex is a reasonable choice of mood stabilizer unless the patient's medical condition indicates hepatic failure. Mania associated with structural damage may respond better to divalproex or carbamazepine [24].

Other considerations in treatment of manic symptoms include tapering and discontinuing the antidepressants if possible. When first-line medication treatment at optimal doses fails to control symptoms, treatment options include addition of another first-line medication. Electroconvulsive therapy can be considered for patients with severe mania, manic symptoms not responding to pharmacologic treatment, and also for treatment of manic symptoms in pregnancy. Also to be considered are the disease-related changes in the pharmacokinetics and pharmacodynamics of the medications, polypharmacy, vulnerability to side effects in already-compromised individuals, and potential side effect profile.

Prognosis

Prognosis varies depending on etiologic disease state. When secondary mania is caused by medications or substances, the behavioral and affective changes usually are reversible. However, when symptoms are caused by CNS injury, neoplasms, infection, or neurodegenerative diseases, manic symptoms may persist.

Conclusions

Mania may present in patients with a variety of medical conditions and requires a comprehensive differential diagnosis. The key to successful treatment of mania in the medically ill is accurate diagnosis with the assistance of history and thorough medical work-up. Once the diagnosis is made, mania needs to be managed effectively. Depending upon patients' characteristics, past history, medical condition, and acuity of the episode, the treatment plan needs to be implemented in collaboration with medical and psychiatric teams. Close attention needs to be paid to the side effects of the medications and drug interactions in the vulnerable medically ill. Although with treatment of underlying etiology, prophylactic treatment may not be necessary in most patients presenting with secondary mania, follow-up is required in patients who are high risk or in patients who have residual symptoms.

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References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders,* edn 4 (text revision edn). Washington, DC: American Psychiatric Association; 2002.
2. Sadock BJ, Sadock VA: **Delirium, dementia, and amnestic and other cognitive disorders** and **Mental disorders due to a general medical condition.** In *Synopsis of Psychiatry.* Edited by Cancro R. Philadelphia: Lippincott Williams & Wilkins; 2003:350–352, 584–586.
3. Shulman KI, Mackenzie S, Hardy B: **The clinical use of lithium carbonate in old age: a review.** *Prog Neuropsychopharmacol Biol Psychiatry* 1987, **11:**159–164.
4. Sibisi CD: **Sex differences in the age of onset of bipolar affective illness.** *Br J Psychiatry* 1990, **156:**842–845.
5. Shulman KI, Tohen M, Satlin A, et al.: **Mania compared with unipolar depression in old age.** *Am J Psychiatry* 1992, **149:**341–345.
6. Shukla S, Cook BL, Muherjee S, et al.: **Mania following head trauma.** *Am J Psychiatry* 1987, **144:**93–96.
7. Gafoor R, O'Keane VO: **Three case reports of secondary mania: evidence supporting a right frontotemporal locus.** *Eur Psychiatry* 2003, **18:**32–33.
8. Glosser G: **Neurobehavioral aspects of movement disorders.** *Neurologic Clinics* 2001, **19:**535–551.
9. Folstein SE, Folstein MF: **Psychiatric features of Huntington's disease: recent approaches and findings.** *Psychiatr Dev* 1983, **1:**193–205.
10. Mendez MF: **Mania in neurologic disorders.** *Curr Psychiatry Rep* 2000, **2:**440–445.
11. Minden SL: **Mood disorders in multiple sclerosis: diagnosis and treatment.** *J Neurovirol* 2000, **6(Suppl 2):**S160–S167.
12. Sadovnick AD, Eisen K, Ebers GC, et al.: **Cause of death in patients attending multiple sclerosis clinics.** *Neurology* 1991, **41:**1193–1196.
13. Jorge RE, Robinson RG, Starkstein SE, et al.: **Secondary mania following traumatic brain injury.** *Am J Psychiatry* 1993, **150:**916–921.
14. Shukla S, Cook BL, Muherjee S, et al.: **Mania following head trauma.** *Am J Psychiatry* 1987, **144:**93–96.
15. Shulman KL, Herrmann N: **Bipolar disorder in old age.** *Can Fam Physician* 1999, **45:**1229–1237.
16. Kilbourne AM, Justice AC, Rabeneck L, et al.: **General medical and psychiatric comorbidity among HIV-infected veterans in the post-HAART era.** *J Clin Epidemiol* 2001, **54(Suppl):**S22–S28.
17.• Nakimuli-Mpungu E, Musisi S, Mpungu SK, Katabira E: **Primary mania versus HIV-related secondary mania in Uganda.** *Am J Psychiatry* 2006, **163:**1349–1354.
Comparative cross-sectional study of patients with primary mania and those with secondary mania associated with HIV.
18. Lyketsos CG, Hanson AL, Fishman M, et al.: **Manic syndrome early and late in the course of HIV.** *Am J Psychiatry* 1993, **150:**326–327.
19.•• Brooks JO, 3rd, Hoblyn JC: **Secondary mania in older adults.** *Am J Psychiatry* 2005, **162:**2033–2038.
Clinical care conference addressing different presentation and treatment strategies for mania in older adults.
20. Meehan K, Zhang F, David S, et al.: **A double-blind, randomized comparison of the efficacy and safety of intramuscular injections of olanzapine, lorazepam, or placebo in treating acutely agitated patients diagnosed with bipolar mania.** *J Clin Psychopharmacol* 2001, **21:**389–397.
21. Daniel DG, Potkin SG, Reeves KR, et al.: **Intramuscular (IM) ziprasidone 20 mg is effective in reducing acute agitation associated with psychosis: a double-blind, randomized trial.** *Psychopharmacology (Berl)* 2001, **155:**128–134.
22. Richard F, Bertschy G, Bondolfi G, Aubry JM: **Possible induction of mania or hypomania by atypical antipsychotics: an updated review of reported cases.** *J Clin Psychiatry* 2004, **65:**1537–1545.
23. Wada K, Yamada N, Sato T, et al.: **Corticosteroid-induced psychotic and mood disorders.** *Psychosomatics* 2001, **42:**461–466.
24. Evans DL, Byerly MJ, Greer RA: **Secondary mania: diagnosis and treatment.** *J Clin Psychiatry* 1995, **56:**31–37.