

Delirium & Delirious Mania; Differential Diagnosis.

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Author: Eline Janszen. (s894226)

Thesis-Supervisor: Ruth Mark

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Department of Neuropsychology, University of Tilburg

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ABSTRACT

In the last few years, delirium in hospitals and in the elderly population has become an important subject of various studies, resulting in the recognition of several subtypes; hyperactive delirium, hypoactive delirium and mixed delirium. The first one of these subtypes, hyperactive delirium, shows a lot of overlap with another syndrome: Delirious mania. The current literature review examines both syndromes, discussing the overlap and the differences of their symptoms, while also looking at the neurological structures involved.

Search engines including Sciencedirect, PSYCHinfo and medline were used to find the relevant literature. The data found in this examination reveals that, in spite of the several overlapping symptoms, delirious mania and hyperactive delirium are different syndromes; hyperactive delirium is associated with symptoms like hyperactivity, circadian rhythm disturbances and neurological abnormalities that include lesions of the hippocampus and dysfunction of the orbitofrontal cortex while delirious mania shows distinctive symptoms like pouring water and denudativeness (disrobing) with neurological abnormalities that also include orbitofrontal cortex dysfunction, but suffer mostly from an overall frontal circuitry dysfunction.

This distinction is important for clinical outcome, seeing as that hyperactive delirium is treated with haloperidol and the preferred treatment for delirious mania is ECT.

Keywords: delirium, hyperactive delirium, delirious mania.

INTRODUCTION

In recent years there has been a lot of research focused on diagnosing delirium. Since patients with delirium display fluctuating symptoms, the distinction from other conditions can be difficult. However, in spite of this work, there has been no study that has yet been able to differentially diagnose hyperactive delirium from delirious mania. This seems odd, seeing as the syndromes are very similar to each other and diagnosis of these syndromes can be mixed up easily. Both syndromes involve an acute onset and a disturbance of consciousness, but tend to differ in manic symptoms like grandiosity and emotional lability and catatonic features. The current review will focus on the differences and similarities between delirious mania and delirium, at both the psychopathological and neurological level.

DELIRIUM

Delirium is a common acute neuropsychiatric syndrome that has been known by clinicians for over 2500 years (Khan, Khan & Bourgeois, 2009). Throughout the years, terms that have been used to describe delirium are; acute brain failure, acute organic brain syndrome, acute confusional state and postoperative psychosis (Gill, 2000). Currently the preferred term is delirium, Diagnostic and Statistical Manual of Mental Disorders (Fourth edition, text revision; DSM-IV-TR) criteria can be found in table I.

Table I: DSM-IV- TR criteria for delirium.

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- Disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with reduced ability to focus, sustain or shift attention.
 - A change in cognition or the development of a perceptual disturbance that is not better accounted for by a preexisting, established or evolving dementia.
 - The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day
 - There is evidence from the history, physical examination or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition.
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SUBTYPES: HYPERACTIVE DELIRIUM

In delirium, three clinical subtypes can be distinguished; hypoactive, hyperactive and mixed delirium (Meagher & Trzepacz, 2000). Patients with hyperactive delirium are agitated, hypervigilant and experience active hallucinations and delusions (more features of the hyperactive subtype can be found in table IV). Patients with hypoactive delirium present lethargy, sedation and slowed motor response. The mixed subtype demonstrates both hyperactive and hypoactive features (Mittal et al., 2011). These subtypes seem to be relatively stable over the course of an episode (Meagher, 2009). This review will look specifically at the hyper-active subtype of delirium, since the overlap in symptoms with delirious mania is especially striking.

DELIRIOUS MANIA

“The outstanding feature of a delirious mania is a nightmarish, dreamlike derealization within an altered sensorium” (Taylor & Fink, 2003, p.51). Delirious mania is a syndrome that, like delirium also involves disorientation and altered consciousness. At the same time it shows characteristics of mania; mania is a mood disorder in which patients feel grandiose and euphoric, they are emotionally instable and very easily distracted, while experiencing racing thoughts (features can be found in table II).

The syndrome delirious mania was first described by Bell in 1849, who wrote about nine patients with disease resembling some advanced stages of mania and fever that was characterized by sudden onset, severe insomnia, disorientation, and extremely bizarre hallucinations and delusions. Since then several authors (Bond, 1980; Mann 1986) have written about the subject, however there is still no clarity on how to categorize it.

Recently Taylor and Fink (2003) proposed that delirious mania is actually a subtype of catatonia (features can be found in table III), characterized by symptoms like excessive motor activity, associated with disorganized speech and confabulation with obvious catatonic features like stereotypy and posturing. Karmacharya, England & Ongur. (2008) found that delirious mania was strongly associated with a history of affective illness, particularly bipolar disorder, and report that these findings suggest that delirious mania is actually a subtype of mania.

As we can understand from these statements, it is unclear whether delirious mania is a subtype of catatonia of mania.

Table II: Observed Symptoms of Mania in Karmacharya et al., 2009.

Severe forms of familiar manic/psychotic symptoms:

- Severe insomnia/total lack of sleep overnight
 - Disorganized behavior (agitation/assault, destruction of property, wandering into others' rooms)
 - Extreme psychomotor agitation (pacing, constant motion)
 - Thought disorder
 - Labile affect (tearful to laughing/screaming in seconds/minutes)
 - Dysphoria
 - Auditory hallucinations
 - Paranoia (fear for own life or those of family, hiding or attempting escape from hospital)
 - No episodic memory for events/behaviors during episode following recovery
 - Pressured speech
 - Requiring physical or chemical restraints
 - Visual hallucinations
 - Hypersexuality/inappropriate touching–groping/public masturbation
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Table III: Principal Features of Catatonia. (Fink & Taylor, 2003).

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- Mutism: Verbal unresponsiveness, not always associated with immobility.
 - Stupor: Unresponsiveness, hypoactivity, reduced or altered arousal.
 - Negativism (Gegenhalten): Patient resists examiners manipulations.
 - Posturing (catalepsy): Maintains postures for long periods, including facial postures.
 - Waxy flexibility: Initial resistance to an induced movement.
 - Stereotypy: Non-goal-directed, repetitive motor behavior.
 - Automatic obedience
 - Ambitendency: Indecisive movement resulting from contradiction by examiner.
 - Echophenomena: Copying despite instruction to the contrary.
 - Mannerisms: Odd, purposeful movements.
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Since there is no clarity on whether to look at catatonic or manic aspects, when faced with delirious mania, throughout this review both syndromes will also be discussed, when relevant to the assessment or treatment of delirious mania . It is expected that both neurological and psychopathological findings will show that delirious mania and hyperactive delirium are in fact different syndromes. We will look at the difference in symptoms, but will mainly focus on the neurological differences. Discussing these differences will help clinicians with making the right differential diagnosis between, hyperactive delirium and delirious mania, and be able to select the appropriate treatment. The different treatments and the importance of this will also be discussed.

METHOD

The articles and data used in this literature study were found using Sciencedirect, PSYCHinfo and Medline search engines. The keywords used were: Delirium, delirium review, hyperactive delirium, subtype(s) delirium, neuroimaging delirium, neurologic delirium, neurotransmitters delirium, delirious mania, Bell's mania, neuroimaging delirious mania, lethal catatonia, catatonia, catatonia, neuroimaging catatonia, neurologic catatonia, neurotransmitters catatonia, mania, bipolar disorder I, neuroimaging mania/bipolar disorder I, neurologic mania/ bipolar disorder I , neurotransmitters mania/ bipolar disorder I. Selection criteria of these articles involved: Population (no case study's) and time of publication.

RESULTS

INCIDENCE

Delirium & Hyperactive Delirium.

The rates of delirium are low in the community (0.4% to 2%) but increase when looking at general hospital admissions (11% to 42%) while in elderly patients, in intensive care units, the incidence of delirium ranges from 70% to 87% (Fong, Tulebaev & Inouye, 2009).

The prevalence of hyperactive delirium has a range of 6-46% among the patients diagnosed with delirium (Stagno, Gibson & Breitbart 2004). It is also been estimated that it accounts for one-fourth of all deliria, suggesting that hyperactive delirium is actually a minority of the deliria that occur (Liptzin & Levkoff, 1992). There seems to be no difference in age, gender, level of physical performance or delirium severity between the subtypes (Boettger &

Breitbart, 2011), although Meagher (2009) found that consultation-liaison populations appear to experience relatively more hyperactivity.

Delirious Mania.

Delirious mania is also thought of as an uncommon syndrome, although Fink (1999) reviewed several studies that suggest that as many as 15- 20% of all acutely manic patients show signs of delirium. A study by Ritchie, Steiner & Abrahamowicz. (1996) on the incidence of delirium among psychiatric inpatients showed that bipolar patients had the highest incidence (35.5%) of developing delirium. Finally, Detweiler, Mehra, Rowell, Kim & Bader. (2009) explained that more than 25% of manic patients have catatonic features and meet criteria for catatonia and that in more than 50% of catatonic patient's features of mania are present.

ASSESSMENT

Hyperactive Delirium.

The classification of delirium subtypes can be based on motoric manifestations or arousal disturbance (Stagno, Gibson & Breitbart, 2004). When looking at the motor aspects of the delirium subtypes, several items of the MDAS, like movement during the interview, can be used to diagnose hyperactive delirium. However, the combination of the MDAS, the Delirium Assessment Scale (DAS) and the new version of the DRS (DRSR-98) provides a more reliable method of identifying clinical subtypes of delirium (Yang et al., 2009). Another way to assess motoric manifestations is the Delirium Motor Checklist (DMC), developed by Meagher, MacLulich & Laurila. (2008), this checklist captures all of the various elements that have been used to define motor subtypes by different methods. Very recently, a new motor subtype scale, the Delirium Subtype Scale (DMSS) has been developed, which focuses only on motor features

that differentiate delirious from nondelirious subjects and shows high levels of predictive validity (Meagher et al., 2011).

The hyperactive symptoms distinguished according to arousal disturbances are: logorrhea (incoherent talkativeness), agitation, stereotyped activities, increased reactivity, delusions, expansive mood, perceptual disturbances and hallucinations, and mental slowing (Stagno, Gibson & Breitbart, 2004).

In both ways of assessing continuous monitoring to detect the fluctuating motor and arousal profile of delirium is important yet challenging (Meagher, 2009).

Delirious Mania.

When assessing delirious mania, it is useful to elicit reports of prior episodes of mood disorder, of a family history of mood disorders, as well as to obtain serum levels of mood stabilizing drugs to rule out intoxication. It is also wise to keep in mind that delirious mania can also be a part of a general medical illness, not directly related to a history of a psychiatric illness (Fink & Taylor, 2003), however Fink (1999) states that the presence of the complex syndrome of mania and delirium, with or without catatonia, justifies the identification of delirious mania, regardless of presumed cause.

If we were to assume that delirious mania falls under the umbrella term catatonia, the following rating scales discussed by Sienaert, Rooseleer & Jurgens (2011) can be used for assessment: Modified Rogers Scale (MRS), Rogers Catatonia Scale (RCS), Bush-Francis Catatonia Rating Scale (BFCRS), Northoff Catatonia Rating Scale (NCRS), Braunig Catatonia Rating Scale (BCRS) and the Kanner Scale. Fink and Taylor (2003) use electroencephalography (EEG), neuroendocrine tests and CPK tests to assess catatonia, while also looking at conditions in which catatonia is expressed (like depression and mania).

When we look at the theory that delirious mania is a subtype of mania, assessing it can be done with the Mania Rating Scale (MRS), proven functional by Youngstrom, Gracious, Danielson, Findling & Calabrese (2003). Altman (1998) reports good results on self-assessment scales in mild to moderate mania, using the Altman Self-Rating Mania Scale (ASRM).

SYMPTOMS

Hyperactive Delirium.

Aside from the usual symptoms seen in delirium, patients with hyperactive delirium show more activity and hallucinating symptoms, a list of this can be found in table IV.

Table IV. Features used for motor subtype definitions. (Meagher, 2009)

Hyperactive features:

1. Increased activity levels
 2. Increased speed of actions
 3. Involuntary movements
 4. Loss of control of activity
 5. Restlessness
 6. Wandering
 7. Increased speed of speech
 8. Increased amount of speech
 9. Loud speech
 10. Abnormal content of verbal output
 11. Hyperalertness/hyperactivity
 12. Distractibility
 13. Fear
 14. Irritability
 15. Euphoria
 16. Uncooperativeness
 17. Combativeness
 18. Nightmares
 19. Hallucinations
 20. Persistent thoughts
 21. Tangentiality/irrelevant talk
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Delirious Mania.

Karmacharya et al. (2008) observed the following distinctive symptoms for delirious mania: Acute onset of severe symptoms, incontinence/inappropriate toileting, denudativeness (disrobing) and pouring water. Other symptoms like insomnia and hallucinations that were also commonly observed, but overlapped with manic/psychotic criteria.

Detweiler et al. (2009, p.24) described the connection between manic, delirious and catatonic symptoms in delirious mania as following: ‘ Manic signs include insomnia, acute excitement, grandiosity, emotional lability; delusions and altered consciousness disorientation characterized by delirium, accompanied by posturing, stereotypy, mutism, negativism and echo-phenomena suggesting catatonia’.

As we can see hyperactive delirium and delirious mania have several overlapping symptoms, making it easy for the clinician to make a wrong diagnosis. Therefore, we will also have a look at other aspects of these syndromes, to make a better distinction.

NEUROLOGICAL ASPECTS OF HYPERACTIVE DELIRIUM

So far the research on the neurological aspects of hyperactive delirium has been limited, although several structural and functional abnormalities can be found, there is little neurological distinction between the subtypes up to this point. Therefore, it is necessary that some of the neurology of the ‘umbrella-term’ delirium is also discussed in the following section.

Structural.

Cell level.

Delirium. Yokota, Owaga, Kurokawa & Yamamoto (2003) found a reduction in deep grey

matter, specifically in the caudate head, thalamus and lenticular nuclei. In spite of the diversity in studies, most of them found more brain atrophy and increased white matter lesions as structural abnormalities in patients with delirium (Soiza et al., 2008).

Brain regions.

Hyperactive delirium. In 1992 Cutting found that lesions of the right cerebral hemisphere were linked with hyperactive delirium. Hyperactive delirium has also been linked with lesions of the cingulate gyrus, the orbitofrontal cortex (which is known to cause restlessness, hyperactivity and disinhibition), hippocampus, parahippocampus, fusiform cortex and lingual gyri (Medina, Rubino & Ross, 1974).

Delirium. A study of cerebral perfusion by Yokota et al. (2003) found that during an episode of delirium, there were bilateral reductions in overall blood flow within the frontal, temporal and occipital areas. Reischies et al. (2005) found that a disturbance of attention and awareness during delirium is related to a dysfunction of an attentional network, involving the anterior cingulate cortex. Finally, Trzepacz (1999) suggested that delirium involved lateralization to the right and a particular neural pathway, responsible for certain ‘core symptoms’ while other symptoms may occur depending on the etiology causing delirium. Neuroimaging reports support this hypothesis; however it is not widely accepted yet.

Functional.

Neurotransmitters.

Hyperactive delirium. Meagher & Trzepacz (2000) found several neurotransmitters involved in hyperactive delirium; in hyperactive delirium there is an anticholinergic activity and TCA side effect (neurotransmitter acetylcholine), increased dopaminergic activity, psychosis and hyperactive disorders (dopamin). Increased serotonergic activity and Serotonin Syndrome was

found when looking at serotonin. H1 receptor activity (histamine), decreased GABA activity and sedative-hypnotic drug withdrawal in Gamma-amino butyric acid. And finally enhanced noradrenergic activity and delirium tremens was found when looking at noradrenalin.

Physiological.

Hyperactive delirium. Van Der Cammen, Tiemeier, Engelhart & Fekkes(2006) found that hyperactive delirium patients had higher plasma HVA levels than hypoactive patients, which is related to psychotic symptoms (Ramirez-Bermudez et al., 2008). Interleukin levels also differ in hyperactive delirium; IL-6 levels are higher, which makes patients more vulnerable to fever (Van Munster et al., 2008).

Balan et al. (2003) found a low level of melatonin in hyperactive delirium, confirming that patients diagnosed with hyperactive delirium suffer from increased disturbances of circadian rhythms. Gupta, Sharma & Mattoo. (2005) also reported that hyperactive patients had greater sleep-wake cycle disturbances and mood lability.

EEG/ Scans.

Hyperactive delirium. Alcohol or sedative-hypnotic withdrawal delirium usually falls into the hyperactive category, and here it is common to find a low-voltage fast EEG (Pro & Wells, 1977). However, other causes of delirium are typically associated with diffuse EEG slowing, regardless of motor presentation (Trzepacz, 1994).

Delirium. Jacobson and Jerrier (2002) showed that an increase of slow EEG activity (delta, theta) and a diminution of the occipital alpha rhythm characterize a delirium. Basal ganglia lesions were found by Figiel, Krishnan, Breitner & Nemeroff (1989) when examining MRI predictors of delirium. Koponen, Partanen, Paakkonen, Matilla, & Riekkinnen(1989) undertook CT brain scans on delirious patients and the outcome suggested that patients with delirium had

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significantly higher indices of ventricular enlargement and an excess of low attenuation, particularly in the parieto-occipital lobes.

Cognition.

Hyperactive delirium.

Perceptual disturbances (e.g., hallucinations) and delusions are more severe in hyperactive delirium, but the overall cognitive functioning according to the memorial delirium assessment scale(MDAS) item scores showed no difference between the subtypes in this area (Boettger & Breitbart, 2011).

Delirium. Henon et al. (1999) examined the influence of preexisting cognitive decline on the occurrence of delirium in stroke patients, these cases had greater degrees of cortical atrophy and white matter lesions.

NEUROLOGICAL ASPECTS OF CATATONIA AND MANIA.

Structural.

Cell level.

Catatonia. Although there is no clear psychology of catatonia (and delirious mania as subtype), Fink and Taylor (2003) come to the conclusion that it is a motor dysregulation syndrome; people with catatonia have trouble monitoring their motor behavior. Since catatonia typically resolves fully, the motor system dysfunction is likely to be one of regulation instead of structural loss of pyramidal motor neurons (Fink & Taylor, 2003).

Mania. In manic states, the study of Haldane & Frangou (2004) reported the following: Reduction in regional CBF (in the basal portion of the right temporal lobe), increased rates of white matter hyperintensities and overall changes in CBF. Difference in gray/white matter

distribution, larger third-ventricular volumes and possible increased lateral ventricular volumes were found in a study of structural brain abnormalities by Strakowski et al. (1993).

Brain Regions.

Catatonia. Joseph (1999) found that frontal lobe and basal ganglia-frontal lobe circuitry lesions are commonly observed in catatonia. Fink and Taylor (2003) also conclude that catatonic features are associated with central motor system lesions and frontal circuitry disease. Northoff (2002b) mentions that the ventrolateral prefrontal cortex might be related to altered inhibitory functions in catatonia. Northoff (2002a) found support for the involvement of the motor, affective and cognitive parts of the anterior cingulate, during emotional stimulation in patients with catatonia. Badgaiyan (2002b) explains this as following: “ Since catatonic episodes are often triggered by emotional stimuli, it appears that, because of the activation of the affective part of cingulate, its motor part is excessively inhibited, resulting in the arrest of a motor activity” (p. 579). Marshall (2000) also suggests the involvement of ‘negative motor areas’ like the orbitofrontal cortex and the anterior cingulate.

Mania. When looking at bipolar disorder as a whole, research reports that the prefrontal and anterior cingulated cortices, and amygdalae are implicated, suggesting an abnormal interaction between the amygdale and the ventral/orbitofrontal cortex (Haldane & Frangou, 2004).

Increased brain activity in the left dorsal anterior cingulate and basal ganglia, decreased activity in the orbitofrontal cortex decreased activation and blunted response in the right ventral prefrontal cortex can be found specifically in mania (Haldana & Frangou, 2004).

Blumberg et al. (1999) also reported decreased right rostral and orbital prefrontal cortex activation, which may lead to impaired planning, judgment and insight.

Functional.

Neurotransmitters.

Catatonia. When looking at neurotransmitters, dopamine plays an important part in the frontal circuitry, particularly in the basal ganglia, and has been hypothesized as having a primary role in motor function. It can therefore be associated with catatonia and although the exact working is still unknown, Fink & Taylor (2003) suggest that catatonic states may be associated with decreased dopamine activity. Frontal circuits are also modified by GABA. Supporting this hypothesis is the fact that Lorazepam (GABA- a agonist) is an accepted treatment for catatonia (Wetzel & Benkert 1987). On the other hand, GABA-b agonists induce catatonia (Northoff et al., 1999a).

Mania. Leiva (1990) found reversal of mania by enhancement of brain cholinergic (acetylcholine) activity, suggesting an important role of acetylcholine in mania.

Physiological.

Catatonia. Fink and Taylor found the following laboratory findings: Increased CPK (creatine phosphokinase), a common feature of severe motor syndrome and increased CSF homovanillic acid (HVA) which is related to psychotic symptoms.

Mania. CSF and plasma HVA levels have been found to be increased in mania (Chou et al., 2000).

EEG/ Scans.

Catatonia. Fink and Taylor (2003) found frontal slowing on EEG; increased size of lateral ventricle of cerebellar atrophy on brain imaging; decreased sensory motor cortex functioning and altered laterality on function MRI and SPECT.

Mania. Strakowski et al. (2011) used fMRI to study brain activation in patients with bipolar mania and found a pattern that suggests dysfunction of an extended ventrolateral prefrontal-

amygdala emotion network during mania, leading to blunted region brain responses, to negative emotion cues and abnormal attentional processing that is reflected in impaired task performance. The disruption of this emotional network may contribute to the mood dysregulation in bipolar disorder.

Cognition.

Catatonia. In catatonia cognitive problems in attention, motor and visuospatial functioning can be found (Fink & Taylor, 2003). The support for the frontal-lobe dysfunction (mentioned earlier) found by Joseph in 1999 can be found in the fact that catatonic patients have problems with working memory, decision-making (Gambling task) and visuospatial tasks (Northoff, 2000; 2002a).

Mania. Haldane & Frangou suggest that decreased prefrontal executive control may underlie the cognitive and emotional symptoms of mania. Clark, Iversen & Goodwin (2001) found that measuring verbal learning and sustained attention were powerful indicators of the deficit in mania, with their results on these tests being consistent with a right prefrontal cortex abnormality in the manic state.

NEUROLOGICAL ASPECTS OF MANIA AND CATATONIA: DELIRIOUS MANIA?

Despite the difference in symptoms, the neurology of mania and catatonia actually overlaps on several levels. Both disorders show increase lateral ventricular volumes, abnormal functioning of the orbitofrontal cortex, the basal ganglia and the anterior cingulate, an overall (ventrolateral) prefrontal cortex dysfunction and cognitive problems in attention. These findings suggest that these regions may also be the regions involved in delirious mania, whether it is a subtype of catatonia or a subtype of mania.

When we look at the studies specifically focused on delirious mania, only data on cognition could be found; Patients with delirious mania tend to be poorly oriented for place, date and time, are unable to recall their recent experiences or the names of objects or numbers given to them (Fink, 1999). Fink, Bender & Green (1952) found that patients with delirious mania make gross errors on cognitive dysfunction screening tests, such as ‘draw a clock-face’ and ‘Face-hand’ - tests.

TREATMENT

Hyperactive Delirium.

The treatment of delirium is a multifactorial intervention that requires multiple interventions (Marcantonio, 2008), in spite of the difference in symptoms, the treatment of hyperactive delirium does not differ from the more general treatment of delirium. To support this statement, the study by Platt et al. (1994) that addressed the effectiveness of treatment with haloperidol in different motor subtypes found similar response rates. In addition, Liu, Juang, Liang, Lin & Yek (2004) found the same results for patients with both hypoactive and hyperactive motor subtypes in a retrospective study of risperidone treatment for delirium.

Treating delirium involves identifying the underlying causes for delirium, nonpharmacological and/or pharmacological interventions. Nonpharmacological interventions include frequent reorientation and touching, using clear verbal instructions and making eye contact when talking to patients (Mittal et al., 2011). Marcantio (2008) also mentions that monitoring nutrition and making orienting items available is a effective intervention in treating delirium. Physical restraint may also be useful in reducing anxiety in hyperactive terminally ill patients (Breitbart, 2001).

Pharmacological interventions in delirium are mainly targeted toward the treatment of its underlying causes, but it may also be needed when the patient's behaviors cannot be controlled by nonpharmacological means (Mittal et al., 2011). Haloperidol is the most studied and usually preferred agent for delirious patients (Mittal et al., 2011), the American Psychiatric Association (APA) recommends low-dose haloperidol as a first-line agent in the symptomatic management of delirium episodes. Ozbolt, Paniagua & Kaiser (2008) have also proven that atypical antipsychotics, such as olanzapine or risperidone are a valid alternative and appear to be as effective as typical antipsychotics in the treatment of delirium. Saxena & Lawley (2010) mention that benzodiazepines are usually preferred when delirium is associated with withdrawal from alcohol or sedatives which most likely will present itself as hyperactive delirium.

Meagher et al. (2011), noted greater use of medications, especially antipsychotics, in patients with a relatively hyperactive presentation, which is consistent with the finding that hyperactive subtype patients posing greater difficulties in ward management. It is, of course, preferable to use one drug only, starting with the lowest possible dose and patients should be closely monitored for response and possible side effects (Saxena & Lawley, 2010). Marcantonio (2008) states that the existing data suggests that treating established delirium is less effective.

Delirious Mania.

In 1980 Bond found an effective treatment for delirious mania, combining haloperidol and lithium. However, a study by Cohen & Cohen (1974) reported that this combination might lead to neurotoxic consequences, also known as neuroleptic malignant syndrome (NMS). Since patients with delirious mania can often be unmanageable, treatment with sedatives is often required. However, benzodiazepines and barbiturates are favored over high potency antipsychotic drugs, because they are effective and have smaller risks of inducing NMS (Fink &

Taylor, 2003). Although the APA recommends that benzodiazepines should be avoided in cases that display delirium, an exception can be made for delirious mania. Karmacharya et al. (2008) also found reliable effects for benzodiazepines, especially lorazepam, while clozapine, lithium and valproate were only beneficial in a few cases and took a much longer period of time to work.

The currently favored treatment of delirious mania is electroconvulsive therapy (ECT), reducing the excitement and psychomotor agitation within two treatments and resolving the syndrome within six (Fink, 1999). Taylor & Fink (2003) recommend bifrontal electrode placement with brief-pulse currents. They also mention that at least six ECT should be administered in the first course and that when catatonia is relieved, continuing ECT will usually resolve the mood disorder and psychosis. Karmacharya et al. (2008) found benzodiazepines less reliable than ECT. Danivas et al. (2010) found the same responses to ECT, with a follow up prescription for lithium.

PROGNOSIS

Hyperactive Delirium.

Hyperactive delirium shows the best prognosis for relief of all symptoms compared to the other subtypes (Kobayashi, Takeushi, Suzuki & Yamagushi, 1992) and patients seem to have the shortest hospital stay (O'Keeffe & Lavan, 1999). Different subtypes are associated with particular in-hospital complications, with falling and interference with treatment being more likely in patients with hyperactive delirium (O'Keeffe & Lavan, 1999).

The hyperactive subtype was also associated with greater reversibility of delirium in elderly medical patients (MacDonald & Treloar, 1997). Several other studies (Meagher et al.,

2008b; Lui et al., 1997; Liptzin & Levkoff, 1992) also found that hyperactive delirium has a shorter duration, was more reversible and had a lower mortality rate compared to hypoactive delirium.

Delirious Mania.

Prior to the introduction of ECT in 1934, over 80% of the patients afflicted with delirious mania died within hours or days from exhaustion, coma and cardiovascular collapse (Mann et al., 1986). However, with the advantage of ECT, the chances of recovering from delirious mania within 2 to 12 treatments are pretty solid (Fink, 1999; Karmacharya et al., 2008; Danivas et al., 2010).

DISCUSSION

HYPERACTIVE DELIRIUM AND DELIRIOUS MANIA

Imagine the following scenario: A patient comes into the emergency room, he does not know what day it is or where he is. He seems agitated and repeats most of the questions the nurses ask to him, without understanding what they are about. At the same time he looks tired and his movements seem abnormal. After talking to his sister, you learn that these symptoms suddenly occurred after the patient had been running a fever for a few hours. Most likely, the patient will receive a diagnosis for delirium, perhaps even for the hyperactive subtype. The preferred treatment in this case will involve a pharmaceutical intervention with haloperidol and/or atypical antipsychotics. But what if this patient is actually suffering from delirious mania? The use of haloperidol or resperidone might induce a neurotoxic response, leading to neuroleptic malignant syndrome, making the patients acutely ill.

This scenario explains why it is so important to make a differential diagnosis between hyperactive delirium and delirious mania. As we have seen, both syndromes do have a lot of overlapping symptoms. And, when we look at the brain regions involved, this overlap is not so strange. Because of the dysfunction of the orbitofrontal cortex, both syndromes show restlessness, impaired planning and problems in judgement. The overlapping psychotic symptoms (delusions and hallucinations) can be explained by the higher plasma HVA levels. A dysfunction in the anterior cingulate cortex can also be found in both syndromes, explaining the problems in attention and the problems with modulating an appropriate emotional response.

Because we do not know if delirious mania should be diagnosed as mania or catatonia, the overlap with these syndromes and delirium might be important to look at, even though we cannot make any statements about it. In hyperactive delirium and mania, dysfunctions in the right cerebral hemisphere can be found, which might make it the dominant hemisphere for these syndromes. In catatonia and delirium, basal ganglia lesions are found, which has an important role in motor functioning and could explain the excessive and stereotyped movement in both syndromes.

In spite of these overlaps, the data we have found in this study does confirm that delirious mania and hyperactive delirium are in fact different syndromes and that different treatment is required. A summary of this data can be found in table V, which can also be used to make a differential diagnosis.

Table V: Differential Diagnosis.

Delirious Mania	Hyperactive delirium
Symptoms:	Symptoms:
- Increased speed of actions	- Catatonic features
- Hyperactivity	- Incontinence/ inappropriate toileting
- Combativeness	- Denudativeness
- Circadian rhythm disturbances	- Pouring water (over floor or head)
- Uncooperativeness	- Hiding in small spaces
Structural:	Structural:
- Brain atrophy, white matter lesions	- Prefrontal cortex dysfunction
- Lesions of hippocampus, parahippocampus, fusiform cortex and lingual giri	
Functional:	Functional:
- Decreased GABA and acetylcholine activity	- Decreased dopamine activity
- Increased dopamine and serotonin activity	- Abnormal GABA activity
	- Gross errors on cognitive dysfunction tests
Treatment:	Treatment:
- Haloperidol	- Benzodiazepines and barbiturates
- Atypical antipsychotics	- ECT

CONCLUSION

Although a lot is still unknown about both hyperactive delirium and delirious mania, the neurological differences alone make it clear that we are, in fact, dealing with two different syndromes. Therefore, they should be treated differently. As we have seen earlier, the best treatment for a delirium involves pharmacological interventions with haloperidol and frequent reorientation, touching, verbal instructions and orienting items. In delirious mania on the other hand, ECT-treatment is preferred, since haloperidol might induce neuroleptic malignant syndrome, which can be fatal to a patient.

The difference in treatment and most of all treatment response, demonstrates the importance of proper diagnosing when dealing with delirious mania or hyperactive delirium. In this study, several limitations can be found. The most important is of course the lack of actual neurologic data or imaging of the brain in delirious mania. Although Fink & Taylor (2003) provide this in their book on catatonia, we would have to assume that delirious mania is a subtype of catatonia.

Seeing as there are still different views on this, it would not be right to just accept this hypothesis. Another important limitation is the fact that it is a literature study. When dealing with syndromes that are still relatively unknown, it would have been better to do an actual patient study to confirm the differences between hyperactive delirium and delirious mania. Finally, this study involves 4 syndromes (catatonia, mania, hyperactive delirium, delirious mania) that are relatively understudied, few reviews and articles were found when researching the neurology of these syndromes. Therefore, the data in this study is based on limited findings. Extended research could provide more clarity and perhaps different findings on this subject.

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