PAYING THE ULTIMATE PRICE

MANIA WITH DEPRESSIVE SYMPTOMS

Date of preparation August 2015

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FOREWORD

We would like to thank you for taking the time to read this report. We, a group of global psychiatrists, suicidologist, patient group representatives and carers of those affected by bipolar I disorder, have developed this report to highlight the cost and mortality associated with mania with depressive symptoms, a common and debilitating form of bipolar I disorder. The devastation and high prevalence of suicidality within thispatient community cannot be underestimated: society, patients and caregivers frequently pay a heavy price in terms of loss of life, emotional burden and physical costs.

Bipolar I disorder is an area where expert understanding is continually evolving. In recent years, bipolar I disorder has been re-defined through recognition that manic and depressive symptoms can occur concurrently. It affects over two thirds of people diagnosed with bipolar I disorder.[1] It is at this point that these patients are at their most vulnerable with 44–54% having considered or attempted suicide.[2,3] Armed with this foresight, it is critical that we intervene to provide urgent and appropriate treatment to prevent unnecessary hospitalisations often costing healthcare economies billions and potentially save thousands of lives worldwide.

Suicide has been made a global imperative by the World Health Organisation, and it is essential that we look to raise awareness of the risk of suicidality in patients affected by bipolar disorders on the global health agenda. This report and 'Call to Action' addresses the direct and indirect costs associated with bipolar I disorder and mania with depressive symptoms due to increased risk of suicidality. It is intended that this report will help improve understanding of the burden of mania with depressive symptoms, and in the long-term, reduce the ultimate price frequently paid by patients and their caregivers around the world.

Signed,

Professor Eduard Vieta (lead report author)

Professor Andrea Fagiolini

Professor Michael Berk

Professor Roger McIntyre

Professor Olavo Pinto

Professor Allan Young

Doctor Umberto Albert

Doctor Jose M Goikolea

Professor Maurizio Pompili

EXECUTIVE SUMMARY

Despite an improved understanding of bipolar I disorder and in particular mania with depressive symptoms, many challenges remain including a lack of public awareness and an increased suicide risk. Mania with depressive symptoms exerts a significant burden on society and is typically diagnosed in young adults, therefore incurring high costs in terms of productivity.

One of the major factors associated with a loss of productivity amongst people affected by bipolar I disorder, and specifically those who experience depressive symptoms during an episode of mania, is a high risk of suicidality (both completed and attempted.)[1,2,4,5,6,7,8] In fact, incidence of suicide attempts amongst this group of patients is four times higher than during other phases of the illness.[9]

The monetary cost of caring for people with bipolar disorders is high; in Europe this can exceed €21.5 billion,[10] whilst in the USA figures are approximately $151 billion per annum.[11]

In addition, the indirect costs of bipolar disorders are known to be four times greater than direct costs, placing a significant burden on healthcare systems and society.[11,12]

This report calls for an improvement in diagnosis and management of mania with depressive symptoms as well as greater support around the associated risk of suicide.

> ***"Bipolar I disorder has a dramatic effect on those living with the condition and understanding the symptoms is crucial to improved diagnosis and management. The significant proportion of patients having feelings of depression during a period of mania highlights the complex nature of bipolar I disorder and the need for greater understanding of the condition."***
>
> ***Rebecca Müller, Treasurer, Global Alliance of Mental Illness Advocacy Networks (GAMIAN) Europe***

The following 'Call to Action' has been developed to reduce the costs associated with mania with depressive symptoms:

1. Improve levels of education and awareness of bipolar I disorder and mania with depressive symptoms to ensure appropriate treatment of this disorder, improve the quality of life for patients, reduce suicidality and the financial burden on society

2. Ensure broader recognition of anxiety, irritability or agitation as the key warning signs of mania with depressive symptoms amongst healthcare professionals to reduce under diagnosis and misdiagnosis and potentially save lives

3. Encourage healthcare professionals to routinely assess and consider depressive symptoms during mania in order to provide the most timely and appropriate treatment and help reduce the serious implications of mania with depressive symptoms

4. Conduct further research based on latest diagnostic criteria (DSM-5) to further enhance knowledge regarding episodes of mania with depressive symptoms in bipolar I disorder as well as look to further quantify the indirect costs of this severe form of bipolar I disorder

5. Initiate broader conversation on the risk of suicide associated with bipolar I disorder and mania with depressive symptoms; help to dispel the persisting stigma and support people affected

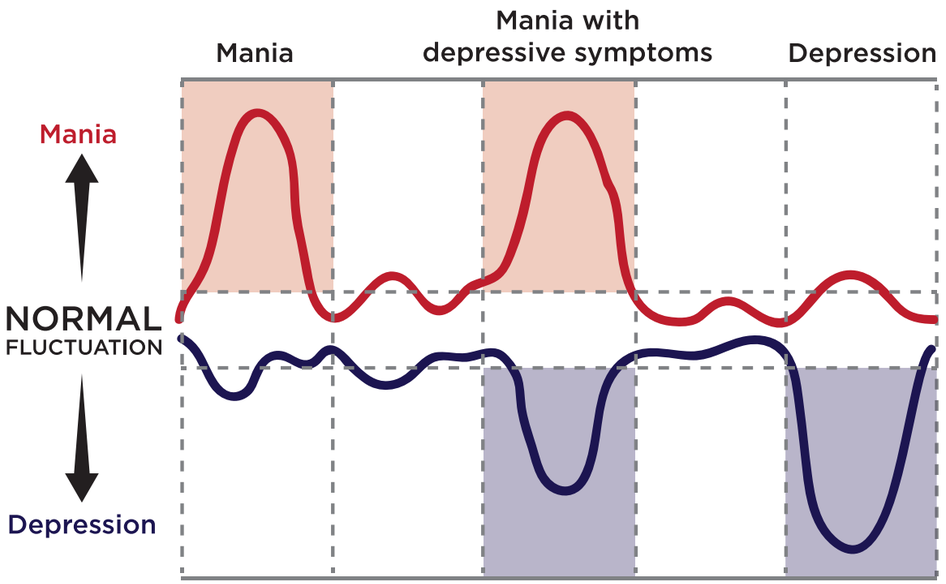
6. Improve support and resources for patients and their caregivers who have been touched by suicide as a result of bipolar I disorder and mania with depressive symptoms. Collaborate to develop a validated suicide risk assessment tool specifically for those diagnosed with bipolar I disorder affected by episodes of mania with depressive symptoms

BIPOLAR I DISORDER AND MANIA WITH DEPRESSIVE SYMPTOMS

Bipolar disorder (formally referred to as 'manic-depressive' disorder) affects close to 30 million people worldwide, including four million in Europe.[13] Globally, it is one of the leading causes of disability[13] and is associated with an increased risk of suicide.[1] From a healthcare professional point of view, bipolar disorder represents around 2-3 out of every 10 patients seen by a psychiatrist.[14]

Bipolar I disorder is a chronic illness characterised by episodes of mania and depression.[15] Patients typically display some or all of manic and depressive symptoms, such as: feeling high or overly happy, extreme irritability or agitation, adopting high-risk behaviours, overly long periods of feeling sad or hopeless, problems concentrating, experiencing anxiety, thinking of death or suicide, or attempting suicide.[16]

> *"Mania with depressive symptoms is a severe form of bipolar I disorder. 64 per cent of patients experience at least one depressive symptom during an episode of mania, while 39 per cent report three or more depressive symptoms. These patients rarely experience symptom free periods and are at a hugely elevated risk of suicide. Effective management and greater awareness is required to ensure the suicide risk and consequences of a suicide attempt are minimised in people affected by mania with depressive symptoms."*
>
> ***Professor Olavo Pinto, Faculty member, Brazil***



Kraepelin. Psychiatrie: Ein Lehrbuch für Studierende und Ärzte, Psychiatrie. 6th ed., Leipzig; 1899; Weygandt. Über die Mischzustände des Manisch-depressiven Irreseins, Munich; 1899

BIPOLAR I DISORDER AND MANIA WITH DEPRESSIVE SYMPTOMS

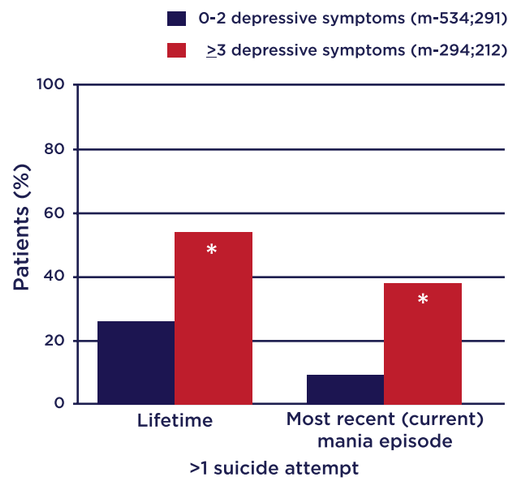
During episodes of mania, depressive symptoms often occur concurrently, with rare intervening periods of 'remission'. These symptom free periods are relatively (but not fully) symptom-free and residual depressive symptoms often occur between episodes.[17] 'Mania with depressive symptoms' is a severe form of bipolar I disorder[1] and is considered to be high-risk for suicidal behaviour, since depressive emotions such as hopelessness are often coupled with mood swings or difficulties with impulse control.[18]

Bipolar I disorder may be experienced by up to 250,000 Australians over their lifetime[21,22]

> *"... you have all the relentless, agitated drive of mania, but none of the euphoria. Instead, you feel depression's misery and self-loathing. It's the most dangerous condition possible, the one in which the most suicides occur."*
>
> ***Terri Cheney, patient[19]***

Published research has shown that 64 per cent of bipolar I disorder patients will suffer from at least one concurrent depressive symptom during an episode of mania,[1] however, results from a new survey amongst 370 global psychiatrists show that 72 per cent are not aware of the frequency of mania with depressive symptoms.[20] This can have devastating consequences: one study found that 54 per cent of people experiencing mania with depressive symptoms have considered or attempted suicide, compared with 26 per cent of people with 'pure mania'.[2] Whereas another found the rates to be slightly lower, but still alarming at 44 per cent and 12 per cent respectively.[3]

Suicide attempts in patients with 0-2 or ≥3 depressive symptoms



n-values in key refer to lifetime and current episode datasets, respectively
*Two-sided t-test, p 0.05 vs 0-2 depressive symptoms group
Young AH, Eberhard J. Neuropsychiatr Dis Treat. 2015;11:1137-1143.

BIPOLAR I DISORDER AND MANIA WITH DEPRESSIVE SYMPTOMS

Mania with depressive symptoms can be identified in several ways. Anxiety, irritability or agitation are important warning signs which also indicate the presence of depressive symptoms within an episode of mania.[1] Almost three quarters (72%) of patients who experience mania with depressive symptoms suffer from anxiety, irritability or agitation.[1]

Mania with depressive symptoms is recognised by the new DSM-5 (Diagnostic and Statistical Manual of Mental Disorders) diagnostic criteria as an important characteristic of bipolar I disorder. This diagnostic tool can be used by healthcare professionals to help identify patients' experiencing mania with depressive symptoms.

> *"Typically we see greater morbidity, younger age of onset, more episodes and shorter intervals between episodes amongst bipolar I disorder patients experiencing mania with depressive symptoms. These patients are more likely to attempt suicide than during a purely manic episode and have a higher number and longer duration of hospitalisations."*

Professor Michael Berk, Faculty member, Australia

Patients affected by mania with depressive symptoms face even greater challenges than during purely manic episodes. Compared to mania without depressive symptoms, concomitant depressive symptoms during an episode of mania is associated with:[1]

- **Higher rates of suicide**
- **More frequent episodes of longer duration**
- **More frequent relapses**
- **A longer time to reach symptomatic remission**

> *"Anxiety, irritability or agitation are seen significantly more in mania with depressive symptoms than in mania alone, and these symptoms could help the physician recognise and identify patients suffering from mania with depressive symptoms."*

Dr Umberto Albert, Faculty member, Italy

> *"It is important to ensure that patients experiencing mania with depressive symptoms have access to treatments which rapidly control depressive symptoms and decrease the suicide risk to ensure that life threatening consequences and hospitalisations can be avoided."*

Dr Jose Goikolea, Faculty member, Spain

DIRECT COSTS OF MANIA WITH DEPRESSIVE SYMPTOMS

THE COST OF CARING

Mania with depressive symptoms in patients diagnosed with bipolar I disorder is both life-threatening and costly. The total cost of bipolar disorder (of which mania with depressive symptoms is a severe form[1]) in the US has been estimated at $151 billion per annum[11], with $7 billion attributed to direct costs.[23] People experiencing mania with depressive symptoms represent up to two thirds of this patient population[1] and are almost three times more likely to be hospitalised.[24] In addition, people affected by mania with depressive symptoms are at a four-fold increased risk of suicide,[9] compared to other phases of illness.

The average direct cost of an Italian bipolar patient after an acute episode is €9,681. Of which;[25]

- **45% of direct costs are attributable to hospitalisation**
- **20% of direct costs are attributable to medical treatment**
- **19% of direct costs are attributable to psychiatric visits**

Approximately 32% of bipolar I patients in Italy have attempted suicide[26]

> *"Suicide is a personal tragedy which causes profound pain and long lasting psychological trauma for both families and friends. On average, a single suicide affects a minimum of six family members and friends. From an economic viewpoint, attempted suicides have a serious hospitalisation and treatment cost impact. There can also be a considerable increase in associated lifetime costs related to disability and premature death. Sadly, episodes of mania with depressive symptoms contribute greatly to global suicide incidence and it is essential that that this severe form of bipolar I disorder is better recognised."*

Kevin Jones, Secretary General European Federation of Associations of Families of People with Mental Illness (EUFAMI)

> *"There is a lack of education, awareness and understanding amongst psychiatrists and other healthcare professionals around suicide risk and prevention in bipolar I disorder patients, specifically those who experience mania with depressive symptoms. The key is to recognise patients experiencing mania with depressive symptoms and stabilise their mood through medication. So often patients experiencing mania with depressive symptoms, are treated with antidepressants which is like adding fuel to a fire."*

Professor Maurizio Pompili, Suicidologist, Italy

DIRECT COSTS OF MANIA WITH DEPRESSIVE SYMPTOMS

ATTEMPTED SUICIDE

According to the World Health Organisation, 1.53 million people will die from suicide in the year 2020, with 10 – 20 times more people attempting suicide.[27] On average this represents one death every 20 seconds, and a suicide attempt every 1-2 seconds.[27] Mental health disorders are associated with more than 90 per cent of all cases of suicide,[28] and this is especially dangerous and life-threatening in bipolar I patients suffering from mania with depressive symptoms.[1] In these patients, the risk of suicide is coupled with mania with depressive symptoms being challenging to diagnose and treat effectively.[29]

"For those experiencing mania with depressive symptoms, the sense of hopelessness of depression combined with the recklessness and hyperactivity of mania too often leads to the devastation of suicide, depriving patients of a long and productive life, while family and friends are left to cope with the grief and loss."

Professor Roger McIntyre, Faculty member, Canada

"Psychiatrists are often afraid to broach the topic of suicidality with their patients. The subject is still seen as taboo and they are uncomfortable or fearful they may 'plant the idea' into a patient's head. This is sadly the opposite of what patients need; discussing suicidality can often be preventative. Patients need a combination of intervention and human support, it is therefore vital that psychiatrists ask and understand WHY patients either want to attempt suicide or have attempted suicide. This is a question that is rarely asked by healthcare professionals but how can you move forward when you haven't understood why it happened in the first place?"

Professor Maurizio Pompili, Suicidologist, Italy

"For 22 years my sister's and I have cared for our brother. During the onset of his diagnosis he attempted suicide five times and experienced severe depression. Ten years later, he experienced stages of euphoria and spent all of his savings. This had a detrimental effect on the family – we worried for his well-being and felt helpless, scared of prompting another suicide."

Anonymous carer, Spain

It is estimated that $358 million is spent on mental health in Brazil per annum[32]

Almost 50% of Brazilian bipolar I disorder patients attempt suicide[33]

DIRECT COSTS OF MANIA WITH DEPRESSIVE SYMPTOMS

HOSPITALISATIONS

Amongst patients diagnosed with bipolar disorders, suicide rates are more than 20 times higher than in the general population,[29] and this costs both lives and money. The average cost following a suicide attempt in someone diagnosed with bipolar I disorder is approximately $25,000 within the first year.[32] A significant proportion of these costs (20 per cent) are incurred within the first month of a suicide attempt; these immediate costs are mostly attributed to emergency and inpatient hospital expenditures.[32]

Hospitalisation costs are particularly high in people affected by mania with depressive symptoms: it is acknowledged that patients experiencing episodes of mania coupled with depressive symptoms have much longer hospital stays than those with pure depressive or manic episodes.[34] In general, for every suicide death, there is estimated to be five hospitalisations and 22 emergency department visits for suicidal behaviour.

"The direct costs of suicide and attempted suicide alone are huge, involving emergency services, hospital care, counselling and support for the patient, their loved ones and others affected by the incident. The highest cost and burden, of course, is in terms of emotional suffering and staggering pain, both for the person who takes his or her life and for the family and people who are left behind. So much of this expenditure could be saved with improved recognition and management of these high-risk patients."

Professor Andrea Fagiolini, Faculty member, Italy

The average direct cost of a Spanish bipolar I patient experiencing mania with depressive symptoms is €4,771 per episode. Of which;[31]

- **77% of direct costs are attributable to hospitalisation**
- **14% of direct costs are attributable to medical treatment**

Approximately 25% of bipolar I patients are unemployed in Spain

"Sadly, in the UK, the numbers of suicides are increasing. In 2013 alone there were 6,233 suicides in the UK, an increase of 4% from the previous year. Whilst these cannot all be attributed to mania with depressive symptoms, the increase is a worrying trend. Despite the known increase in suicides, mental health trusts in England are forecasting significant cuts to their funding over the next four years. This reinforces the urgent need for psychiatrists to recognise and acknowledge vulnerable patients suffering from disorders such as mania with depressive symptoms quickly, in order to treat them effectively."

Professor Allan Young, Faculty member, United Kingdom

More hospital beds in Canada (8%) are occupied by people with bipolar disorder than by sufferers of any other medical condition[35]

INDIRECT COSTS OF MANIA WITH DEPRESSIVE SYMPTOMS

INDIRECT VS DIRECT COSTS

The indirect costs associated with bipolar I disorder, and specifically mania with depressive symptoms, are extensive, spanning loss of productivity due to morbidity and premature death and financial implications, as well as intangible costs due to the impact of the disease (for example pain, grief and suffering). Although direct costs such as hospitalisations are expensive, the indirect costs of bipolar disorders, including episodes of mania with depressive symptoms, are even higher; in fact these are estimated to be four times greater.[11,12]

Indirect costs associated with bipolar I disorder and specifically mania with depressive symptoms do not simply impact a patient, but the community surrounding them, from care givers, family members and healthcare professionals.[36]

One sixth (16.5 per cent) of indirect costs associated with bipolar disorders are incurred by lost productivity of family members and caregivers.[36]

> *"The costs associated with suicidality in bipolar I disorder patients, especially those experiencing mania with depressive symptoms, is extremely high. When they are admitted to hospital following a suicide attempt they need a lot of assistance from medical doctors, surgeons, nurses, psychiatrists, psychologists and then there are the rehabilitation costs. The impact on their family can be devastating. The stress and worry can become all encompassing; they don't want to leave their loved one on their own due to the suicide risk, which can impact the carer's ability to work. Additionally, many carers pay privately for numerous consultations with psychiatrists which can put a lot of strain on their finances."*
>
> ***Professor Maurizio Pompili, Suicidologist, Italy***

> *"For over half of my daughter's lifetime I have cared for her during phases of mental illness – it is a lifelong job. During her first episode of mania with depressive symptoms my daughter was hospitalised for 18 months in both closed and open wards. It was a terribly chaotic time, I'd never before heard of anybody who was mentally ill let alone cared for someone. I feared for her life; we were without a clear diagnosis and I needed to be with her 24 hours a day. Over time I became extremely stressed and fell into depression myself."*
>
> ***Anonymous carer, Sweden***

INDIRECT COSTS OF MANIA WITH DEPRESSIVE SYMPTOMS

> *"Caring for someone with bipolar I disorder, particularly during an episode of mania with depressive symptoms, is a constant balancing act to support them whilst maintaining relationships and family life. Episodes of mania with depressive symptoms not only affect the patient but their network of family and friends, it has placed unimaginable stress on my family unit, pushing my husband and I close to divorce and straining our relationship with our other daughter and her family. Before an episode of mania with depressive symptoms my daughter has often become irritable and anxious, screaming at her children and being hospitalised. It is difficult to put into words how challenging this is to witness."*
>
> ***Anonymous carer, Sweden***

> *"Caring for someone with bipolar impacts on all aspects of a person's life. This includes relationships, finances, and ability to work. Carers can become very isolated from friends and family members. Frequently we see that carers have to work part time or quit paid employment altogether in order to care for their loved one. On top of a reduced income, they may be financially supporting their loved one, such as providing money for rent or paying fines and debts. Carers' physical and mental health also suffers, and this includes high rates of depression and anxiety. We need more services and support for carers, in their own right. When carers are supported, they are able to provide higher quality care to the person they love."*
>
> ***Carer patient advocacy group, Australia***

> *"The anxiety of not knowing if or when the symptoms would escalate to disastrous levels was very preoccupying, and interfered with my ability to concentrate at work. Insomnia and lack of sleep during these times also impacted work in a very negative way."*
>
> ***Anonymous carer, Canada***

INDIRECT COSTS OF MANIA WITH DEPRESSIVE SYMPTOMS

IMPACT ON SOCIETY

People with bipolar I disorder rarely experience symptom free periods.[17] Between the severe mood episodes, patients often have residual symptoms, which contribute to impaired functioning.[37] In a survey conducted by the Depression and Bipolar Support Alliance (DBSA), almost nine out of every ten people with bipolar I disorder said it had affected their job performance.[38] More than half surveyed said they thought they had to change jobs or careers more often than others and many felt they were either given less responsibility or passed up for promotions.

> *"The effect of a suicide attempt on a patient is very complicated. Whilst some recover from it and are able to work, the vast majority are left with a profound scar in life, especially when they don't receive adequate emotional support. These patients often have trouble finding and keeping jobs and are at increased risk of multiple suicide attempts."*

Professor Maurizio Pompili, Suicidologist, Italy

> *"My wife currently has a poor credit rating due to spending sprees in the distant past. Dire overspending many years ago led to periods of poverty and homelessness."*

Anonymous carer, Canada

> *"Mania with depressive symptoms has heavily affected my brother during his lifetime. People in the community don't understand bipolar I disorder, making integration very difficult for him. The stigma attached to bipolar I disorder has prevented my brother from finding a job, which is a shame as employment would help him to achieve personal autonomy whilst improving his self-esteem."*

Anonymous carer, Spain

Specifically, in terms of episodes of mania with depressive symptoms, unemployment is higher in or amongst these patients, compared to those with 'pure mania' (49 per cent versus 26 per cent).[39] In addition, bipolar I disorder patients with mania and depressive symptoms in outpatient care are known to have higher unemployment rates than depressed patients (42 per cent versus 36 per cent).[40] Research has also shown that amongst patients with depressive symptoms there is a tendency for a higher number of days off work, which confirms the greater functional impairment compared to patients with pure mania.[41]

INDIRECT COSTS OF MANIA WITH DEPRESSIVE SYMPTOMS

IMPACT ON CARE GIVERS

> *"Caring for my daughter during episodes of mania with depressive symptoms has affected all aspects of my life; from work to my relationship with my husband and our finances. It is an expensive illness – when she was first diagnosed with bipolar I disorder I was forced to give up my job in order to care for her. Such episodes also trigger erratic behaviour, where she shops for things she cannot afford. I am retired now but continuing to pay for my daughters debts from my pension, as without my help, I fear she will face further financial consequences. Sometimes my husband and I have been so fed up and tired we talk about emigrating, but know of course this is not an option for us."*

Anonymous carer, Sweden

> *"There have been incidents in the past that had a profoundly negative impact on my life. These included times when I was depressed and sad and angry for months. My wife's irritability was also very difficult to handle, even when her symptoms did not meet clinical criteria for an episode of mania with depressive symptoms. This is important to understand, because often the friend/family member may feel something is wrong with them, or that they're doing something wrong to provoke the prickly behaviour. But that's usually not the case. There's a lashing outward during an episode of mania with depressive symptoms, whereas the negativity is directed inward, towards the self, during purely depressed states."*

Anonymous carer, Canada

Indirect costs for bipolar disorder in the US are estimated to be $38 billion annually; this includes lost productivity of both the patients and their care givers.[30] The cost impact of suicide is also not only limited to hospitalisations; 14 per cent of total lifetime indirect costs of bipolar disorder are attributable to productive life years lost and lost earnings due to suicide.[42]

Bipolar disorder (including mania with depressive symptoms) can result in damaged relationships and difficulty working, or participating in regular activities.[16] As well as affecting work lives and relationships, it can also have a profound impact on the wellbeing of people with the condition. It is understood that three quarters of patients (76 per cent) experience a decrease in their own expectations of success in life because of their bipolar I disorder, while 79 per cent say it has had a negative impact on their physical health.[43]

> *"During her first episode of mania with depressive symptoms my daughter attempted to take her own life. I feel unable to describe the impact attempted suicide can have; from unanswered questions, challenging my ability as a parent and craving for her to become better. My husband and I found it increasingly difficult to communicate, we were like zombies, it was an incredibly tough time."*

Anonymous carer, Sweden

> *"We understand the long lasting and damaging effects of suicide, attempted suicide and frequent hospitalisations have on patients' families and carers and call for the bipolar community to better acknowledge mania with depressive symptoms."*

Rebecca Müller, Treasurer, GAMIAN Europe

CONCLUSION

Bipolar I disorder, and particularly mania with depressive symptoms, is an underestimated and expensive global health issue. The costs of mania with depressive symptoms are due to long term indirect costs associated with co-morbidities, suicide, early death and unemployment, coupled with frequent hospitalisation during episodes. Bipolar I disorder can worsen if it is left undiagnosed and untreated. Episodes may become more frequent or severe over time without treatment, while delays in getting the correct diagnosis and treatment can contribute to financial, social, work-related problems and even death.

Suicide is a leading cause of death across the world, and a significant proportion of this is related to mental illness and specifically mania with depressive symptoms. The impact of suicidality in people affected by episodes of mania with depressive symptoms cannot be underestimated; society, patients and caregivers all pay a heavy price in terms of loss of productivity, healthcare costs and the impact on quality of life. It is imperative that we help to ensure correct and timely diagnosis as well as appropriate treatment, to help patient's lead healthy and productive lives whilst in the long term, reducing the associated suicide risk and hospitalisations.

THE FOLLOWING 'CALL TO ACTION' HAS BEEN DEVELOPED TO REDUCE THE COSTS ASSOCIATED WITH MANIA WITH DEPRESSIVE SYMPTOMS:

1. Improve levels of education and awareness of bipolar I disorder and mania with depressive symptoms to ensure appropriate treatment of this disorder, improve the quality of life for patients, reduce suicidality and the financial burden on society
2. Ensure broader recognition of anxiety, irritability or agitation as the key warning signs of mania with depressive symptoms amongst healthcare professionals to reduce under diagnosis and misdiagnosis and potentially save lives
3. Encourage healthcare professionals to routinely assess and consider depressive symptoms during mania in order to provide the most timely and appropriate treatment and help reduce the serious implications of mania with depressive symptoms
4. Conduct further research based on latest diagnostic criteria (DSM-5) to further enhance knowledge regarding episodes of mania with depressive symptoms in bipolar I disorder as well as look to further quantify the indirect costs of this severe form of bipolar I disorder
5. Initiate broader conversation on the risk of suicide associated with bipolar I disorder and mania with depressive symptoms; help to dispel the persisting stigma and support people affected
6. Improve support and resources for patients and their caregivers who have been touched by suicide as a result of bipolar I disorder and mania with depressive symptoms. Collaborate to develop a validated suicide risk assessment tool specifically for those diagnosed with bipolar I disorder affected by episodes of mania with depressive symptoms

GLOSSARY OF KEY TERMS

- **Bipolar disorder:** (also known as manic-depressive disorder) a chronic, episodic illness so named because sufferers alternate between two poles of extreme moods - mania (which may include symptoms such as episodes of elevated moods, extreme irritability, decreased sleep and increased energy) and depression (which may include overwhelming feelings of sadness and suicidal thoughts), or a combination of both[44]

- **Bipolar I:** a sub-type of bipolar disorder. It is defined by the presence of mania or mania with depressive symptoms. These intense moods often lead to problems with daily functioning, interference in personal relationships, and extreme behaviours such as suicide attempts[43]

- **Bipolar II:** a sub-type of bipolar disorder. It is characterised by severe depressive episodes alternating with episodes of hypomania[43]

- **Depression:** a state of low mood and aversion to activity that can affect a person's thoughts, behaviour, feelings and sense of well-being. People with depressed mood can feel sad, anxious, empty, hopeless, helpless, worthless, guilty, irritable, ashamed or restless[43]

- **Direct costs:** medical costs such as expenditures for diagnosis, treatment, continuing care and rehabilitation

- **DSM (Diagnostic and Statistical Manual of Mental Disorders):** the Diagnostic and Statistical Manual of Mental Disorders is a classification and diagnostic tool in the area of psychiatry developed by the American Psychiatric Association (APA)[43]

- **Indirect costs:** lost productivity due to morbidity and premature death, and intangible costs (e.g. pain, grief and suffering)

- **Mania:** an extreme and intense state of elevated mood and high activity/energy level that can affect people's thinking and judgement. It can make it difficult or impossible to deal with life in an effective way. A period of mania can affect both relationships and work[43]

- **Suicide:** self-inflicted death with evidence (either explicit or implicit) that the person intended to die[45]

- **Suicide attempt:** self-injurious behaviour with a nonfatal outcome accompanied by evidence (either explicit or implicit) that the person intended to die[45]

- **Suicide ideation:** thoughts that serve as the agent of one's own death[45]

A meeting was hosted by H. Lundbeck A/S in March 2015 with the MANIA[64] faculty, to gain their advice and insights regarding the content of the report. In addition, H. Lundbeck A/S conducted a literature review to investigate the costs and the impact of suicidality associated with bipolar I disorder and mania with depressive symptoms. H. Lundbeck A/S has also facilitated the review of this report amongst all stakeholders involved.

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