

THE IMPORTANCE OF DEPRESSIVE MIXED STATES IN SUICIDAL BEHAVIOUR

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DEPRESSZÍV KEVERT ÁLLAPOTOK JELENTŐSÉGE SZUICID MAGATARTÁSBAN

A kutatások eredményei arra utalnak, hogy a depresszív kevert állapotok (DMX) jelentős szuicid rizikófaktort jelentenek a major affektív epizód során. Számos újabb vizsgálat igazolta, hogy a depresszív kevert állapot az unipoláris major depressziósok egyharmadánál, a bipoláris II major depressziós betegek kétharmadánál van jelen, és jelentősen fokozza az öngyilkosság veszélyét. Ezt az állapotot jellege és jellemzői miatt a bipoláris spektrum részének kell tekintenünk. Emellett a depresszív kevert állapotok felismerése és ismerete az öngyilkosság felismerése és megelőzése szempontjából is lényeges. Jelen cikk célja az öngyilkossági kísérlet / befejezett öngyilkosság és a depresszív kevert állapotok (DMX, major depresszió és három vagy több egyidejű nem eufóriás hipomán tünet a depresszív epizód során, ami nagyon közel áll a jól ismert „agitált depresszióhoz”) közötti összefüggés áttekintése. Cikkünk három fontos következtetést állapít meg a depresszív kevert állapot és a szuicid viselkedés összefüggésével kapcsolatban: 1. Az öngyilkosságok nagy része során major affektív epizód áll fenn; 2. A depressziós kevert állapot és az agitált depresszió az öngyilkos viselkedés rizikófaktora; 3. A depresszív kevert állapotot és az agitált depressziót a bipoláris spektrum részének kell tekinteni. A fentebbieket figyelembe kell venni a hangulatzavarban szenvedő betegekkel végzett klinikai és diagnosztikus munka során.

KULCSSZAVAK: öngyilkosság, depresszív kevert állapot, agitált depresszió, bipoláris spektrum zavar

SUMMARY

Research indicates that depressive mixed state (DMX) constitutes a very important suicide risk factor within the major affective episode. Several recently published studies demonstrated that DMX is present in one third of unipolar- and in two thirds of bipolar II major depressives, and substantially increases the risk of suicidal behaviour. Because of its nature and characteristics, this condition should be considered as part of the bipolar spectrum. The recognition and better understanding of DMX also have important implications for the recognition and prevention of suicide. The aim of this manuscript is to review the relationship between suicide attempt / completed suicide and depressive mixed state (DMX) (major depression plus 3 or more co-occurring intra-depressive non-euphoric hypomanic symptoms, which highly correspond to the well-recognised “agitated depression”). Our review establishes three important key points related to the role of depressive mixed states in suicidal behaviour: 1. In the majority of suicides, a current major mood episode is present; 2. DMX and agitated depression present a risk factor for suicidal behaviour; 3. DMX and agitated depression should be considered as bipolar spectrum. These should be taken into consideration in clinical and diagnostic work with affective disorder patients.

KEYWORDS: suicide, depressive mixed states, agitated depression, bipolar spectrum disorder

INTRODUCTION

As a complex, multicausal behaviour with a strong bio-psycho-social and cultural foundation, suicide is associated with several psychiatric and demographic risk factors of varying importance and diagnostic benefit (Goodwin & Jamison, 1990; Rihmer et al., 2002). Suicide is one of the most important treatment outcomes of major depression. Suicidal behaviour is a heterogeneous concept involving suicidal ideation, suicide attempt and completed suicide. The risk factors for attempted and completed suicide show only a few differences and as we know, suicide attempt is one of the most powerful predictors of committed suicide (Angst et al., 2005; Balazs et al., 2003; Beautrais et al., 1996; Goodwin & Jamison, 1990; Hawthorn & van Heeringen, 2000; Rihmer et al., 2006; Rihmer et al., 2009). In this paper the risk factors for attempted and completed suicide are discussed together.

Psychological autopsy studies and other clinical research on suicide attempters consistently show that more than 90% of suicide victims/attempters have at least one Axis I psychiatric disorder, with (mostly untreated) major depressive episode (59-87%), substance use disorder (10-15%) and schizophrenia/schizoaffective disorder (10-18%) (Angst & Angst, 1990; Angst et al., 2005; Balazs et al., 2003; Beautrais et al., 1996; Cheng et al., 2000; Conwell et al., 1996; Hawton et al., 2003; Hawton et al., 2005; Henriksson et al., 1993; King et al., 2001; Rihmer et al., 2006; Rihmer et al., 2002; Tondo et al., 2003).

In the currently used classification systems (Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) and International Classification of Mental and Behavioral Disorders 10th Edition (ICD-10)) there are two major types of affective disorders: unipolar depressive disorder and bipolar disorder. Bipolar disorder is divided into bipolar I (BP-I) disorder (manic and major depressive episodes) and bipolar II (BP-II) disorder (hypomanic (but not manic) and major depressive episodes). In contrast to manic episodes of BP-I patients, hypomanic episodes of BP-II patients shouldn't require hospital care for this condition and shouldn't cause marked impairment of function (Goodwin & Jamison, 1990).

Untreated or unsuccessfully treated major depressive episode is the major cause of attempted and completed suicide, especially if other risk factors are also present (Rihmer & Akiskal, 2006). It

is important to underline, that although major depression is very common among suicide attempters and victims, not all patients with a major depressive episode commit suicide. Therefore there are specific conditions within a major depressive episode which predispose for suicide. In case of unipolar depressive and bipolar patients, suicide occurs most frequently (78-89%) during a major depressive episode, less frequently during mixed (dysphoric) mania (9-20) and nearly never during euthymia (Isometsa et al., 1994; Rouillon et al., 1991; Simpson & Jamison, 1999; Tondo et al., 2003).

The risk is different in case of different types of affective disorders. Studies contradict each other whether unipolar or bipolar depression carries the higher risk for suicide (Rihmer, 2005; Tondo et al., 2003), which can be explained by different study designs and different diagnostic procedures (e.g., various follow-up times, prospective or retrospective nature of the study, clinical versus research diagnoses, index versus follow-up diagnoses), but most importantly by considering (or not) the specific diagnosis of BP-II, the quite common form of bipolar disorders, that, in several important dimensions, takes an intermediate position between classical BP-I and unipolar major depression (Angst et al., 2005; Benazzi, 2006; Benazzi & Akiskal, 2003; Rihmer & Angst, 2005). Another source of this contradiction could be the unresolved nosological position of bipolar spectrum disorder („unipolar” major depressive episode with means unipolar depression with bipolar family history, or with cyclothymic/hyperthymic pre-morbid personality, antidepressant-associated mania/hypomania in major depression). Unrecognised bipolar depressives treated with antidepressant monotherapy (without concomitant use of mood stabilizers) may worsen the condition and in rare cases it is able to induce aggressive or self-destructive behaviour (Rihmer & Akiskal, 2006).

Although suicide is greatly associated with mood disorders, it is currently viewed as a state-dependent phenomenon as suicidal behaviour is very rare in the absence of major mood (mostly depressive) episode (Rihmer & Akiskal, 2006; Rouillon et al., 1991; Szanto et al., 2003; Tondo et al., 2003; Williams et al., 2006). On the other hand, however, as only a small proportion of major depressives commit suicide other psychiatric and psycho-social suicide risk factors should also play a role (Rihmer et al., 2002).

SUICIDAL BEHAVIOUR AND DEPRESSIVE MIXED STATES

The past few years brought new insights to the nature and relationship of bipolar disorders. It has been described that there are three main types of clinical manifestations of overlapping symptomatology in affective disorders: 1. mixed affective episode, with the full concurrent syndromal existence of mania and major depression; 2. dysphoric mania, where during a full manic syndrome at least 2 depressive symptoms are present; and 3. depressive mixed state (DMX), characterized by at least 3 non-euphoric hypomanic symptoms in a full major depressive episode (Table 1). Intradepressive hypomanic symptoms are most frequently irritability, crowded or racing thoughts, psychomotor agitation and talkativeness.

Table 1. Clinical manifestations of overlapping symptomatology in affective disorders

Mixed affective episode	Dysphoric mania	Depressive mixed state
Full concurrent syndromal existence of mania and major depression	Full manic syndrome + at least two depressive symptoms	Full major depressive episode + at least 3 non euphoric hypomanic symptoms

As early as 1899, already Kraepelin observed the emergence of a number of manic or hypomanic symptoms within a major depressive episode, a phenomenon which he described as “excited depression”. Kraepelin also noted that “depression with flight of ideas” was a depressive mixed state, where the thought disorder characteristic of mania (flight of ideas, racing or crowded thoughts) emerged as a symptom of opposite polarity from depression. Furthermore, he also considered recurrent depression without any past history of mania as “manic-depressive insanity”, on the one hand because of its recurrent nature, and because manic episodes could develop later, and on the other hand because he observed that manic symptoms were often present inside depression (Akiskal & Benazzi, 2003; Benazzi, 2006; Koukopoulos & Koukopoulos, 1999). Kraepelin noted that inpatients were more likely characterized by severe excited thought disorder, and in outpatients rather mild depressive mixed states were present, primarily with intradepression irritability and restlessness indicating the “manic foundation” of their illness. In the same time, in 1898 Hecker referred to mild depressive states as cyclothymia

which corresponds to what we term today BP-II depression (Koukopoulos & Koukopoulos, 1999).

The presence of three or more intradepressive hypomanic symptoms results in depression with psychomotor agitation. Agitation is well-known to be a significant risk factor for suicide (Bush et al., 2003), and thus both agitation and DMX increases suicidal ideation and the risk of suicidal attempts in unipolar and bipolar patients both in clinical and community samples (Benazzi, 2005; Perugi et al., 2001; Sato et al., 2005; Sato et al., 2003; Szadoczky et al., 2000). According to one study, mild agitated depression was present in 20% of strictly diagnosed unipolar major depressive outpatients (Akiskal et al., 2005).

There are several factors arguing for the bipolar nature of DMX, such as bipolar family history, younger age of onset, higher number of recurrences, atypical depression, and the similarity of factor structures of hypomania occurring inside and outside of depression (Akiskal & Benazzi, 2003; Benazzi, 2003; , 2005; Benazzi & Akiskal, 2001; , 2003; Bottlender et al., 2004). Several findings point to the bipolar origin of mixed depressive episodes. Depressive mixed states occur frequently in BP II disorder (50-60%) and also often in unipolar major depression (25-30%) (Benazzi, 2006). DMX seems to have moderate inter-episode stability (Sato et al., 2004) and the recent finding that unipolar depression with DMX has a seasonal pattern similar to bipolar and different from unipolar depression (Sato et al., 2006) also supports the bipolar nature of mixed depressive episodes. In psychiatric outpatients DMX and agitated depression are greatly overlapping conditions suggesting that agitation is either the consequence or the part of intra-depressive hypomanic symptoms. This also supports the view that agitated depression in unipolar patients indicates a bipolar spectrum disorder (Akiskal & Benazzi, 2003; Akiskal et al., 2005; Benazzi, 2006).

It has now come to the focus of attention that DMX might constitute an important risk factor in depression. It has also been described that suicide attempts and suicidal ideation occurs with a much higher frequency in mixed depressives (Benazzi, 2005; , 2006; Maj et al., 2003; Perugi et al., 2001; Sato et al., 2003).

Some of the bipolar markers, such as bipolar family history among first degree relatives, atypical depression, and DMX occur significantly more frequently in agitated than non-agitated pa-

tients and current suicidal ideation is present in a significantly higher part of agitated patients than non-agitated patients (62% vs. 43%) (Akiskal et al., 2005; Benazzi, 2006). Agitated depression seems to be robustly associated with DMX, especially suicidal ideation, psychomotor activation and racing / crowded thoughts, which again argue for the classification of agitated unipolar depression and unipolar depression with racing / crowded thoughts as a bipolar mixed state part of the bipolar spectrum. Agitation and racing / crowded thoughts in depressive mixed states are important suicide risk factors when present in unipolar major depression (Akiskal et al., 2005).

Several studies have compared the frequency of suicide attempts and suicidal ideation in mixed and non-mixed major depressives. Dilsaver et al (2005) investigated adolescents with a current major depressive episode (unipolar depressed: 140 + bipolar depressed: 100). Among girls (but not for boys) they found a strong association between suicide attempt and DMX: girls with DMX had more than four times higher risk of having suicide attempt, than patients having non-mixed major depression. In a most recent study, we aimed to investigate the clinical characteristics and frequency of DMX in 100 consecutive nonviolent suicide attempters (Balazs et al., 2006). We found that DMX was present in 63% of the total sample and in 79% among the depressive suicide attempters, and in patients with mixed depression, irritability, distractibility and psychomotor agitation was present in 90% of the cases. DMX was present in 90% of bipolar suicide attempters and 62% of non-bipolar suicide attempters. In comparison, in case of nonsuicidal outpatients, DMX is present in 59% of BP-II and 27% of unipolar major depressive patients (Benazzi, 2003). These results suggest that suicide attempters come mainly from mixed bipolar and unipolar major depressives and also support the association between suicide and DMX (Akiskal et al., 2005; Benazzi, 2005; Perugi et al., 2001; Sato et al., 2003).

The better understanding of the nature of depression by identifying its different forms and classifying them as part of the bipolar spectrum is one of the major advances of contemporary psychiatry (Akiskal & Benazzi, 2003; Benazzi, 2005; Perugi et al., 2001; Sato et al., 2003). This new view cast on the nature of these disorders has several therapeutic implications as well. Antidepressant monotherapy unprotected by mood stabilizers, especially in case of bipolar or bipolar spectrum patients can give rise to hypomanic/manic switches and rapid cycling, but what is more important, it can both worsen the existing mixed state or generate “de novo” mixed conditions, which may lead to treatment resistance, deepening on depression and ultimately suicidal behaviour (Akiskal et al., 2005; Benazzi, 2005; Rihmer & Akiskal, 2006).

CONCLUSION

It's well known, that in the case of unipolar depressive and bipolar patients, suicide occurs either during a pure or mixed major depressive episode or mixed (dysphoric) mania nearly never during euthymia (Rouillon et al, 1991, Isometsa et al, 1994, Simpson and Jamison, 1999, Tondo et al, 1999). The existence of DMX supports the continuum approach as a concept of mood disorders. These findings provide further evidence that mood disorders can be viewed as a spectrum disease. Considering our present knowledge on suicide risk reviewed above the better understanding, description, recognition and appropriate treatment of DMX can be a major step in suicide prevention.

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