# Conversion from Unipolar to Bipolar Depression

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## Abstract

Many studies have demonstrated that major depressive disorder has a tendency to convert to bipolar disorder, although it is possible that a reverse shift is masked by treatment. Conversion from unipolar to bipolar disorder generally takes place at a rate of 1% per annum but this may be higher in younger cohorts. Many factors predict conversion, including family history, symptomatology, personality and, in female patients, trigger by childbirth. Clinicians should therefore be aware of the possibility of conversion and conscious of the risk factors.

Key words: bipolar disorder, major depressive disorder, conversion, switching, depression

## Presence of Conversion

The first question to ask when approaching this topic is whether unipolar depression does ever become bipolar disorder. Various studies claim to have testified to this phenomenon (1) as cited in (2), (3), (4), (5). In each of these, cohorts of patients with a confirmed diagnosis of major depressive disorder (MDD) were followed up and any change in their diagnosis to bipolar disorder noted. Akiskal et al. noted that in such studies the conversion rates to bipolar I (BP-I) vary from 0% to 37.5%, median 9.7% (1). There are several possible reasons for this large range of reported conversion rates. A particular potential methodological criticism of these studies, is that, since bipolar disorder consists of both depressive and manic (or hypomanic) episodes, a bipolar individual whose first episode happens to be depressive might receive a diagnosis of MDD before they experience their first episode of mania or hypomania; this would result in an apparent conversion due to a premature diagnosis of MDD. If the conversion took place within the first year of the depressive episode, the diagnosis of bipolar disorder might be easier to make and the confusion with the diagnosis of MDD would be less likely to occur; however, in longer studies it has been shown that the conversion sometimes takes place much later than 12 months after the initial depressive episode. A study by Goldberg et al. followed 74 adults who were hospitalised with unipolar depression over 15 years, demonstrating that conversions took place over the entirety of this period (6). Since robust diagnostic criteria were used in many of these studies, there appears to be good evidence to support that this was a genuine conversion from MDD to bipolar disorder rather than mere correction of misdiagnosis.

What is also interesting in this phenomenon is that conversion not only takes place from unipolar to bipolar depression but that it occurs between the smaller diagnostic entities within these conditions. In an important recent study, it was shown that patients with bipolar disorder not otherwise specified or cyclothymia tended to progress to BP-II, while those diagnosed with BP-II could convert to BP-I (7). It is possible that, rather than the MDD-BP conversion being a distinct event, it is the overriding direction of a continuous conversion along the unipolar-bipolar spectrum. It is, nevertheless, intriguing that this conversion is unidirectional; that is, it is common for MDD to become BP, but the reverse does not appear to take place. The reason for this is not obvious and should be subject to further research. One possibility is that it is merely an artefact of psychiatric medication and diagnosis, for it is not improbable to suppose that if a patient has reached the criteria for bipolar disorder but at some subsequent point ceases to experience manic or hypomanic episodes, the clinician will tend to assume that this is due to the effect of continuing mood stabilisers on their condition rather than considering that one facet of their illness had improved. This critique may have some merit, but a

helpful historical study by Angst and Sellaro, which discussed the natural history of bipolar prior to the introduction of mood stabilisers and antidepressants, notes poignantly that 'bipolar disorder has always been highly recurrent and considered to have a poor prognosis' (8). Hence, it is likely that there does exist a genuine preponderance in affective disorders away from unipolar depression and towards bipolar disorder.

## Chronology of Conversion

We have already discussed how conversion from unipolar to bipolar depression does not always occur immediately; it is now appropriate to examine in greater detail how these conversions are distributed over time. In a study of outpatients with MDD, conversion took an average of 6.4 years from the start of the follow-up, with a range between 1 and 25 years (5). In fact, Akiskal et al. demonstrated that there is a conversion rate of around 1% each year in a study of 559 patients with MDD, who had a mean age in the low thirties at the start of the study (9) as cited in (2). It is not the case, however, that this rate is constant regardless of the study group, for Goodwin and Jamison have noted that this figure only applies to a mature cohort: in children and younger adults, conversion can be as high as 3-5% per annum (10). It would appear then that younger patients are in a more volatile state and should require a lower index of clinical suspicion for conversion than depressive adults.

The other aspect of conversion chronology to be considered is its relationship to the onset of depressive symptoms. In our own study (11), we conducted a retrospective analysis of 128 patients with confirmed bipolar disorder to ascertain the onset of depressive and (hypo)manic symptoms, based on patient reports. We found that there was a mean delay of 7.3 years (SD=7.9) from the onset of depressive to the first (hypo)manic symptoms. The variance of this figure demonstrates that the moment of conversion is not easily predicted, even when the time of first depressive symptoms is known. Since the first diagnosis given to many of these patients was MDD rather than BP, it is likely that this delay accounts for a diagnostic lag. In short, while much of the literature has already demonstrated that bipolar is a possible outcome for MDD, our study shows that MDD is also the most likely precursor to bipolar disorder, even if it is not always given this diagnosis.

## Predictors of Conversion

While the actual time of conversion is highly variable, there are certain features of MDD patients that increase the statistical likelihood of switching to bipolar. In an important paper by Akiskal et al., in which 206 outpatients with depression switched to bipolar, six criteria were identified as being significant predictors of conversion, as follows: onset at or before 25 years of age, BP family history, strong family history of affective illness, precipitation by childbirth, hypersomnia with psychomotor retardation, and pharmacological mobilisation (5). The specificity of any one of these variables was poor, but taken together, any 3 of them gave an impressive diagnostic specificity of 98%. The authors poignantly note that conversion 'tends to be limited to certain predisposed individuals with primary affective disorder'. The place of post-partum mental illness of any type as being liable to convert to bipolar has more recently been verified by a large study in which 14% of women with post-partum symptoms converted, while only 4% of the other women in the trial did so (12).

In addition to these predictors, other factors have been identified which may be elicited by a careful history and examination. First, bipolar-like symptoms among unipolar depressives have been implicated in predicting conversion. In particular, sub-threshold hypomanic symptoms are significant in identifying individuals who will switch, with a reduced need for sleep, unusual energy and increased goal-directed activities being important factors (13). Furthermore, patients with transient manic symptoms in the presence of MDD have higher rates of conversion than those who have MDD without these symptoms (14). Second, pre-conversion personality has convincingly been shown to be significant in this regard, at least in conversion to BP-II. Akiskal and colleagues showed that patients who converted from MDD to BP had scored higher on neuroticism, orality, emotional reliance and were lower on ego resiliency and emotional stability; these authors also identified four new personality factors (mood lability, energy-activity, daydreaming and social anxiety), which similarly apportioned higher scores to BP-II converters. The authors memorably noted the 'intimate interweaving of trait and state', as they showed the importance of the clinician not limiting patient history taking to features that were clearly pathological. What was interesting about this research was that it showed no difference whatsoever between non-converters and BP-I converters (1). Since

other studies have not made this distinction, it still remains to be seen if other predictors of conversion demonstrate a similar disparity.

## Conclusions

From the published studies it is clear that MDD does convert to bipolar disorder, possibly passing through various sub-classifications en route. Moreover, although it is hard to predict when a patient will convert, a number of factors, related to their age, symptomatology, personality and family history can be very accurate predictors of the likelihood of conversion taking place. Clinicians should be aware of these factors when treating depressive patients, anticipating the possibility of conversion and managing it appropriately if it does occur. Research is now required to take this practice to the next level by formulating neurobiological predictors of conversion, as it is likely that combining neuroimaging and genetic analysis with clinical measures would yield still greater accuracy.

## GP Comment

### What have I learned from this paper?

Patients who initially have what appears to be a clear diagnosis of depression may "convert" to bipolar disorder and this could have important implications for treatment. Those who have a diagnosis of depression need to be followed up and specific enquiry must be made about hypomanic or manic symptoms.

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