Is underdiagnosis the main pitfall when diagnosing bipolar disorder?

Daniel Smith and **Nassir Ghaemi** believe that many people with bipolar disorder remain undiagnosed, but **Mark Zimmerman** argues that overdiagnosis is the bigger problem

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YES Bipolar disorder is a complex condition, and patients can present with the entire range of psychiatric symptoms.[1] Its underdiagnosis has always been, and continues to be, a major problem.

Ever since Emil Kraepelin defined manic depressive insanity as recurrent mood episodes (either mania or depression, but not necessarily requiring mania) in 1898,[2] the condition has been underdiagnosed. For almost a century it was commonly misdiagnosed as schizophrenia.[3] In 1980, the *American Diagnostic and Statistical Manual* (DSM-III) narrowed the definition of schizophrenia and divided manic depressive insanity into two groups: broadly defined major depressive disorder and narrowly defined bipolar disorder.[4] Reasons for underdiagnosis since then include lack of insight into mania by patients, lack of systematic assessment of mania by clinicians, stigma, and the aggressive marketing of antidepressants. The broadening of the definition of bipolar disorder to include hypomania in 1994 and marketing of new drugs have begun to address a century of relative neglect; yet, perhaps predictably, objections about overdiagnosis have been raised.

Defining misdiagnosis

Let's start by agreeing on some definitions. Overdiagnosis implies that a disorder is frequently diagnosed when absent, as well as when present. Underdiagnosis, conversely, implies that a disorder is often not diagnosed when present and also infrequently diagnosed when absent. Underdiagnosis and overdiagnosis are claims of validity (based on a definitive diagnosis from pathological findings or, in psychiatry, a formal research diagnostic interview[5]) not reliability (whether clinicians agree on what they have diagnosed). We should therefore start with certain knowledge about diagnosis (from a research interview, not clinicians' diagnoses) and assess the accuracy of earlier diagnoses, not the other way around. Stated simply, poor reliability means only that clinicians could not agree on the diagnosis. It says little about true rates of misdiagnosis.

In Zimmerman and colleagues' widely cited study,[6] 43% (63/145) of patients who

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NO Bipolar disorder is a serious illness resulting in significant psychosocial morbidity and excess mortality. Research reports, reviews, and commentaries have suggested that bipolar disorder is under-recognised, and that many depressed patients have, in fact, bipolar disorder.[1-4] The treatment and clinical implications of the failure to recognise bipolar disorder in depressed patients include the underprescription of mood stabilising drugs, an increased risk of rapid cycling, and increased costs of care.[5-8]

During the past decade, my hospital has introduced semistructured diagnostic interviews into outpatient clinical practice. Use of these interviews initially documented underdetection of psychiatric comorbidity,[9-11] and these findings were replicated in other settings.[12-14] However, in recent years, we observed the emergence of an opposite phenomenon in bipolar disorder—clinician overdiagnosis in patients without a history of a manic or hypomanic episode.

"Overdiagnosing bipolar disorder can unnecessarily expose patients to serious drug side effects"

Overdiagnosis is the bigger problem

We therefore conducted a study to determine how often bipolar disorder might be overdiagosed and underdiagnosed.[15] We interviewed 700 psychiatric outpatients with the structured clinical interview for DSM-IV (SCID), a widely used, validated, diagnostic interview. About a fifth of the sample reported having had bipolar disorder diagnosed (145, 21%), significantly higher than the number we diagnosed with the structured interview (90, (13%), P<0.001). Only 63 (43%) of the 145 patients who reported a previous diagnosis of bipolar disorder had the condition diagnosed by the structured interview. Bipolar disorder was also underdiagnosed in some patients, but three times as many patients had been overdiagnosed as had been underdiagnosed (82 *v* 27).

Supporting the validity of our diagnoses of bipolar disorder, we found that the patients who were previously wrongly diagnosed with bipolar disorder were significantly less likely to have a first degree relative with bipolar disorder than patients who were accurately diagnosed with bipolar disorder.

answered "yes" to a questionnaire item ("Have you been diagnosed with bipolar or manic depressive disorder by a healthcare professional?") subsequently had bipolar disorder diagnosed by formal research interview. This suggests only that the earlier diagnoses were unreliable (which is unsurprising given that these diagnoses were made by different health professionals using different diagnostic criteria over long periods of time). This kind of disagreement among clinicians and researchers does not prove overdiagnosis because it does not begin with findings on validity.

Validity and reliability

We carried out the required validity analysis based on the research interview data from that same study. According to the formal research interview, 90 patients had bipolar disorder and 610 did not.[6] Thirty per cent (27) of patients with true bipolar disorder had not been previously diagnosed whereas only 13% (82) of those without bipolar disorder had previously had the condition diagnosed. In effect, bipolar disorder had been missed more than twice as frequently as it was mistakenly diagnosed (relative risk 2.23, 95% confidence interval 1.53 to 3.25). Unfortunately, low reliability in this study was reported as evidence of overdiagnosis when in fact the (validity) data suggest underdiagnosis.[6]

We have found no study reporting overdiagnosis that started with definitive diagnoses and compared these with earlier clinical diagnoses. Studies that have reported overdiagnosis in substance abuse[7 8] or adolescents[9] actually describe only low reliability because, as with the Zimmerman study, they start with a relatively unreliable measure of diagnosis (routine clinical practice) and then compare this with the formal research assessment.

In contrast, four studies that used the validity approach all identified underdiagnosis (40-67% of patients with bipolar disorder were previously misdiagnosed).[10-13] These include detailed case series studies of adults with mood disorders[10 11] and substance abuse[12] and in children.[13] Although sample sizes in these studies were smaller (pooled n=271 versus n=700 in the Zimmerman study), they were not less rigorous in design because all misdiagnosis studies must retrospectively assess previous diagnoses. Taken together, these studies (as well as the Zimmerman study when fully and correctly analysed) are strong evidence of underdiagnosis of bipolar disorder.

"Studies that have reported overdiagnosis actually describe only low reliability"

Low diagnostic reliability is not unique to bipolar disorder because all psychiatric diagnoses have, at best, only moderate reliability[14] and complex psychiatric disorders may be difficult to diagnose without necessarily implying overdiagnosis. Diagnostic disagreement is common in other disorders that are known to be underdiagnosed—for example, asthma,[15] dementia,[16] chronic cholecystitis,[17] and coeliac disease.[18] These are all, like bipolar disorder, unreliably diagnosed.

In summary, although clinicians' diagnoses of bipolar disorder can be unreliable, this does not contradict the reality that if patients truly have bipolar disorder they are more likely to be missed than correctly diagnosed. Underdiagnosis, not overdiagnosis, remains the major problem for bipolar disorder within contemporary clinical practice.

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The proportion with affected relatives in the overdiagnosed patients was the same as in patients who never had bipolar disorder diagnosed.

Although other studies have reported overdiagnosis of bipolar disorder, we are aware of only one other study with data on both overdiagnosis and underdiagnosis. Hirschfeld and colleagues[16] interviewed 180 depressed primary care outpatients receiving antidepressant drugs with the structured clinical interview for DSM-IV. Forty three patients reported a prior diagnosis of bipolar disorder, and this diagnosis was not confirmed in 14 (33%). The overdiagnosis rate of 33% was higher than the 22% underdiagnosis rate in the 137 patients who had not had bipolar disorder previously diagnosed.

Thus, the only two studies examining both underdiagnosis and overdiagnosis have both found evidence that overdiagnosis is a greater problem than underdiagnosis.

Accuracy is crucial

Whether bipolar disorder is more frequently overdiagnosed or underdiagnosed is not really important. Rather, it is critical that it is accurately diagnosed. Use of thorough diagnostic evaluations is important to detect bipolar disorder. Consistent with other studies, we found that nearly one third of the patients we diagnosed with bipolar disorder were previously undiagnosed.

However, most discussions of the misdiagnosis of bipolar disorder have focused on the personal and societal costs of underdiagnosis. Only occasionally have authors discussed the possible problems associated with overdiagnosis. Unnecessary side effects are a potentially serious consequence of overdiagnosis. Mood stabilisers are the treatment of choice for bipolar disorder and, depending on the drug, can affect renal, endocrine, hepatic, immunological, or metabolic function. Thus, overdiagnosing bipolar disorder can unnecessarily expose patients to serious drug side effects.

Causes of overdiagnosis

Why might the phenomenon of false positive bipolar disorder diagnoses be arising at this time? One important answer is likely to be the increased availability of drugs to treat bipolar disorder and the accompanying marketing efforts. Many continuing medical education programmes on bipolar disorder begin with a summary of research suggesting bipolar disorder is underdiagnosed, and this is followed by a discussion of methods clinicians can use to improve the detection of the disorder. These discussions of diagnostic practice are usually not balanced by a summary of studies of showing overdiagnosis and the risks associated with overdiagnosis. Because clinicians are probably inclined to diagnose disorders that they feel more comfortable treating, when confronted with patients with mood instability who do not meet criteria for a hypomanic episode, doctors may nonetheless diagnose a potentially drug responsive disorder such as bipolar disorder rather than a disorder such as borderline personality disorder that is less responsive to drugs.

Use of screening scales, such as the mood disorders questionnaire, for bipolar disorder can also result in overdiagnosis. Screening questionnaires prioritise sensitivity, at a cost of false positive results, because it is presumed that they are followed by expert clinical evaluation. Insufficient diagnostic rigour after the use of screening scales can result in greater rates of overdiagnosis. Routine use of bipolar disorder screening scales is not supported by the data and does not make conceptual sense.[17]

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