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Debate section

Letters to the editor

Phenomenology is not enough

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I read with great interest the editorial in the September issue 2010 of the *Acta Psychiatrica Scandinavica* lamenting the current conceptualization of schizophrenia and the related psychotic disorders (1). The authors have correctly identified problems in our formulation of the illness and pointed out that genome-wide association studies have only identified genetic variants with a limited amount of explanatory power. However, I wish to point out that in their review, the authors failed to discuss the role of structural genetic variants (i.e. genetic duplications, deletions and rearrangements) and the risk for developing schizophrenia. These genetic lesions, while individually rare, are collectively more common than previously recognized, and as methods to detect them improve, they will be found even more frequently in the near future. Structural variants can dramatically increase the risk of developing illness with odds ratios as high as 25 reported (2). Importantly, these genetic lesions confer risk for schizophrenia, but not specifically. Affected relatives who share the genetic variant are also at greatly elevated risk for autism, bipolar disorder and other psychiatric illnesses (3, 4). The consensus building from these studies is that there are many biological pathways that can be affected at dozens (if not hundreds) of sensitive loci and that each can predispose an individual to psychiatric illness. How the damage to a particular gene(s) or pathway is translated into one clinically recognizable disorder and not another is currently unknown, but it speaks to the presence of broadly shared genetic risk that cuts across our established diagnostic boundaries of mental illness. Thus, while it is true that the clinical presentation of schizophrenia is heterogeneous and fails in many cases to provide a reliable set of core symptoms, the evidence suggests that this variability may be genetically hard-wired, possibly reflecting an important biological mechanism underlying the disorder. If this is indeed the case, then it may be overly optimistic and ultimately untenable to expect that any single set of symptoms or clinical features, including hebephrenia, will usefully serve as a stable marker of psychiatric illness in the absence of understanding the underlying disease process. Without this insight, even the most careful phenomenological description is incomplete and fails to add value as a diagnostic or prognostic indicator.

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Reply

We are grateful to Dr. McCarthy for his encouraging remarks and agree that it is not possible to design studies of the biological characteristics of 'schizophrenia' under the present DSM rules as these identify heterogeneous samples. It is precisely for complex genetic studies that we offer the means to more homogeneous sampling, thereby increasing the chances of identifying the genetic variants that he anticipates (1). Genetic studies now call attention to factors that confer risk of schizophrenia, but Dr McCarthy notes that '*affected relatives*…are at greatly elevated risk for autism, bipolar disorder and other psychiatric illnesses,' suggesting a non-specific vulnerability, a situation analogous to seeking the genetic risk of 'mental retardation.' Using hebephrenia criteria rather than DSM 'schizophrenia' criteria will increase the likelihood of finding the anticipated genetic markers.

From the historic record and the failure to biologically clearly delineate schizophrenia, we concluded that the construct of schizophrenia was too broad and fatally flawed and re-defined it as hebephrenia. We offer specific cross-sectional and longitudinal diagnostic criteria that include a prodrome of childhood cognitive, emotional, and neuromotor problems, socialization difficulties, and occasional perceptual distortions. In the second or third decade, the sufferer experiences formal thought disorder (paraphasic speech with agrammatisms, derailments, neologisms), delusions of passivity (controlled by outside forces, thought insertion, and withdrawal), auditory hallucinations, loss of emotional expression, avolition (no interests or plans, reduced interactions, apathy), indifference to his present situation, and cognitive deficits. Motor disturbances emerge and chronicity ensues.

Most patients now given the schizophrenia diagnosis do not fit this image of hebephrenia. They reflect several different conditions.

Refining schizophrenia as hebephrenia will identify homogeneous samples that will improve the likelihood of significant

biological findings in genetic and neuroscience studies. We, as does Dr. McCarthy, look to such studies to clarify the biology of the syndromes.

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Lithium addition to a tricyclic antidepressant results in optimal efficacy

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We read with interest the comprehensive article by Spijker and Nolen (1), who discussed the Dutch algorithm for the pharmacological treatment of depression. We agree with their recommendation to promote the use of algorithms in daily practice.

With regard to step 3 of the Dutch algorithm, lithium augmentation, the authors conclude that it is the best-documented strategy for antidepressant non-responders, but they do no mention whether it matters to which antidepressant lithium is added.

However, a tricyclic antidepressant (TCA) (imipramine), with subsequent lithium addition, for patients without remission has been found more effective than a similar strategy with novel antidepressants in two studies (2, 3). In the first comparison (n = 100), imipramine vs. mirtazapine (2), the two-step strategy resulted in 64% response for the imipramine–lithium group vs. 48% for the mirtazapine–lithium group (remission rates were not given). In the second study (n = 138), imipramine vs. fluvoxamine (3), remission rates were 59% for the imipramine–lithium sample vs. 41% for patients receiving fluvoxamine–lithium.

In the STAR*D study (4), the efficacy of lithium was disappointing, with 16% of patients achieving remission after 9 weeks of lithium addition. The low remission rate may be explained by suboptimal dosing of lithium, but may also be because of the fact that lithium was added to a variety of novel antidepressants.

As it seems likely that adding lithium to an antidepressant is performed only once in the algorithm, it is important to realize that adding lithium to a TCA (imipramine) appears to be superior to adding lithium to a novel antidepressant (mirtazapine, fluvoxamine).

Therefore, an algorithm for the pharmacological treatment of depression should include an advice to add lithium to a TCA.

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Reply

We thank our colleague Tom Birkenhäger for his comment on our article. We fully agree that the evidence for lithium augmentation is the strongest for augmentation to a TCA. In the update of the Dutch Multidisciplinary Guideline, 2009 (1), the recommendation for lithium augmentation is also formulated in this way.

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