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Early and delayed treatment of bipolar disorder

Using Danish registry data, Kessing *et al* examined the relationship between lithium response and the timing of treatment (early *v.* delayed).[1] Early treatment was associated with an increased probability of lithium response. This is a clinically important finding, given the increasing emphasis on early intervention in bipolar disorder. The results of the Kessing *et al* study are sobering. Only few patients, particularly among those for whom treatment was delayed, responded to lithium. Several factors may have contributed to the reported results.

The study did not – and possibly could not – control for the cycle shortening that is observed after successive episodes of bipolar disorder. Although the interpretation of such cycle shortening has been debated,[2] it is well established that early cycles are significantly longer than those occurring later; consequently, early in the course of illness one would expect longer spontaneous remissions regardless of treatment. This effect may be partially responsible for the greater treatment response in patients receiving early intervention in the Kessing *et al* study.

Naturalistic studies typically demonstrate full response in about 30% of participants[3] (that is, no recurrences, or the Kessing *et al* criterion, in treatment-adherent patients), which is markedly greater than the response rate observed by Kessing *et al*. This discrepancy could be related to age at first contact. The average age of participants whom Kessing *et al* reported as having received early and late treatment was 46.7 years and 49.1 years, respectively. The natural history of bipolar disorder includes an average age at onset in the second or third decade of life. The trajectory of the illness, where mania typically develops as the last stage, delays the diagnosis of bipolar disorder. Also, there is often a substantial delay in starting treatment even following the diagnosis of bipolar disorder.[4,5] These reports, in conjunction with the advanced age at index presentation, and high rates of antidepressant, antipsychotic and anticonvulsant use in the Kessing *et al* study suggest that participants may have been afflicted with bipolar disorder for some time before 'first contact'. In a sample of 450 participants, Baldessarini *et al* reported a negative relationship between treatment latency and effect of treatment on time spent ill.[5] If the aforementioned findings are generalisable to the Danish sample, the reduced overall treatment responses may be interpreted as a consequence of relatively advanced participant age.

Finally, Kessing *et al* analysed data collected since 1995. Is it possible that participants had received lithium during the years prior? This would further complicate the interpretations of sample responsiveness to lithium, regardless of early or late initiation. In conclusion, we suggest that the findings presented by Kessing *et al* are limited by the lack of control for inter-participant differences in the manifestation of the natural history of bipolar disorder. Such control may be difficult, or in some cases impossible, to achieve using registry-based observational data, but is nevertheless imperative to understanding the effects of early *v.* late treatment prophylaxis in relapsing–remitting illnesses such as bipolar disorder.

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Authors' reply: We are confident that the relatively low response rates to lithium in our study relate to the narrow definition of lithium response, rather than to characteristics of the included patients.[1] Thus, we intended to characterise patients who had an excellent response to lithium monotherapy; that is, patients who were 'cured' from further affective episodes following a start-up period of lithium as in a prior study.[2] We used two robust clinical indicators to define excellent lithium response: (a) lithium prescribed in monotherapy; and (b) no need for psychiatric hospital admission. By doing this, we defined lithium response in a rather rigorous way, resulting in relatively low rates of response. We do not find that our definition of lithium response hampered the finding of the study that early treatment with lithium was associated with increased probability of excellent lithium response compared with delayed treatment, or hampered the generalisability of this finding. Although cycle acceleration occurs on average in bipolar disorder[3,4] the results of our study may suggest that early treatment with lithium might prevent progression of bipolar disorder.

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'Reasonable adjustments' for vulnerable patients

We support the views of Tuffrey-Wijne & Hollins[1] and their argument for the NHS to take an organisational approach to embed documentation and provision of reasonable adjustments for those with protected characteristics under the Equalities Act 2010. Lord Darzi defined quality for the NHS as comprising three dimensions: safety, effectiveness and patient experience.[2] The provision of reasonable adjustments is central to each of these.

Safety – Tuffrey Wijne & Hollins rightly identify the lack of provision of reasonable adjustments as being a patient safety issue. The Confidential Inquiry into Premature Deaths of People with

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