A New Tool to Refine Lithium Therapy:

A Simple Formula for a Complex Problem

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We read with interest the article by Köhler-Forsberg and colleagues,[1] who have developed a straightforward equation to better estimate the level of lithium in the plasma of patients taking this medication. To accurately determine the serum-lithium (se-Li) level, standard procedure is to draw blood 12 hours after the last intake of lithium. However, in practice, it is often difficult to ensure the gap between lithium intake and subsequent blood sampling is precisely 12 hours, as patients do not usually take their medication at a regular time. Further, the timing of the blood test can also vary considerably, and therefore the gap is usually approximately 12 hours and the accuracy of measurements is somewhat compromised. It is because of this inherent imprecision that the authors decided to devise a clinical tool to estimate the 12-hour se-Li level (eLi_{12}) based on the patient's report of when they last took lithium.

To devise their formula, Köhler-Forsberg and colleagues[1] conducted innovative proof-of-concept studies. While we admire their achievements and share their enthusiasm, we wish to add a small note of caution and draw attention to the importance of conducting further research. This is because further studies are necessary to gain sufficient confidence in applying the newly developed tool in clinical practice, especially across varied populations.

While the proof-of-concept studies are elegant in their design and well executed, they only included a modest sample (26 individuals), and this limits the robustness of the findings and their generalizability. However, as noted by the authors themselves, these limitations can be easily overcome by undertaking further studies to replicate these findings in larger and more diverse samples.

In addition, future research should consider several factors that influence plasma lithium levels as outlined both in our previous work and those of others.[2–4] These include, for instance, age, impaired renal function, comedication, and comorbid disorders. Expanding further, lithium clearance decreases with age, which results in lower oral doses necessary to reach plasma levels that are therapeutic.[5] Similarly, impaired renal function, and administration of other medications, often as part of comorbid treatment, can significantly affect lithium clearance and result in the accumulation of lithium in the body.[6]

As regards the precision of the new measure, the authors state that "eLi_{12} provides clinicians with more accurate 12-hour se-Li estimations." This is partly because the new equation shows significantly less variation in relation to the 12-hour se-Li level compared to traditional blood test estimations. Nevertheless, some limitations remain; for example, it is unclear how the absolute dose of lithium impacts the estimation of se-Li levels—indeed, this is not part of the equation. Further, a key constraint is that the formula depends wholly on the patient's ability to recall the exact time of their last dose. This might prove difficult for severely ill patients or those with cognitive impairment. In addition, although the authors acknowledge some of these limitations, it is important to note that even patients with intact cognitive functioning may simply forget or make a mistake in their recall.

Finally, turning to the potential benefits of the tool, its simplification of the monitoring of lithium may assist in promoting the agent among a newer generation of psychiatrists and other prescribers. Lithium is well-known for its efficacy in treatment for bipolar disorder, taking pole position in the majority of clinical practice guidelines and having the unique status as the only "true" mood stabilizer.[7,8] However, over the last two decades, we have observed a substantial decline in the prescription of lithium and its use in clinical practice.[9] This discrepancy between how it should be used, based on its effectiveness, and its actual use in practice is possibly a consequence of unfamiliarity among clinicians and a reluctance to prescribe an agent that requires close monitoring and is seen as more burdensome.[10] Therefore, the development of a new clinical tool might help to raise awareness of the benefits of lithium therapy and, hopefully, encourage practitioners to consider prescribing this core element of the psychiatric pharmacopoeia in their practice.

As regards the advantages of the tool for patients themselves, it also

has the potential to facilitate greater adherence to lithium therapy by making monitoring more manageable. This is because, assuming that the validity and reliability of the tool are corroborated by further research, it will clearly offer greater flexibility as patients are not limited in terms of when they have their blood tested. This in turn is likely to improve lithium's image, which at present is somewhat tarnished by the requirement for regular monitoring of plasma levels[11] both to ensure efficacy and to avoid adverse effects.[12] Importantly, in addition to making monitoring more flexible, comparisons between the US and Denmark health care systems suggest that use of the tool may be generalizable across diverse patient populations—an essential requirement in modern-day societies.

In conclusion, the work by Köhler-Forsberg et al[1] offers a promising solution to the essential but somewhat restrictive practice of monitoring plasma lithium levels. The tool has the potential to make an important difference in the lives of patients on lithium therapy and perhaps increase the uptake of lithium treatment more generally. However, significant further research and refinement are necessary before the tool will be "ready for prime time," and so while it is important to enthusiastically champion this innovative advance, it is equally important to maintain a measured approach to this new measure.

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