Pharmacotherapy for borderline personality disorder: NICE guideline

In their review of drug treatments for borderline personality disorder, Lieb et al., despite considering similar evidence, draw largely different conclusions from those we drew when developing the NICE guideline. Lieb et al recommend a range of drugs. These include anticonvulsants for affective dysregulation symptoms (topiramate, valproate semisodium and lamotrigine) and impulse–behavioural dyscontrol symptoms (lamotrigine and topiramate); and anti-psychotics (aripiprazole and olanzapine) for cognitive–perceptual symptoms. In contrast, we do not recommend drug treatment other than for the treatment of comorbid disorders.

There are a number of reasons for the disparity. First, we did not consider the evidence from some studies to be usable. These trials tended to find large effect sizes favouring treatment compared with effect sizes from other trials. Following further investigation, we considered this evidence for topiramate, lamotrigine or aripiprazole to be unreliable and excluded the trials from our analysis (see p. 218 of the full guideline). Second, most other recommendations made by Lieb et al are based on weak and/or low-quality evidence. We do not agree with the interpretation of the evidence for valproate, which Lieb et al claim shows a reduction in interpersonal problems and depression. The apparent effect on interpersonal problems is derived from a trial of 30 participants with more than 60% drop out. The effect on depression, which we noted as not statistically significant (s.m.d. = −0.61 (95% CI −1.29 to 0.07)), is derived from a larger trial with skewed data, in which over 60% of participants were not diagnosed as having borderline personality disorder. We therefore graded this evidence ‘low quality’.

The authors also claim ‘favourable results’ for haloperidol and the other antipsychotics on symptoms of affective dysregulation, and for omega-3 fatty acid supplementation and flupentixol decanoate. It is unclear for which ‘symptom constellation’ these latter drugs are recommended. We calculated similar effect sizes, but tended to grade the quality of evidence ‘low’ because of single studies, skewed data and wide confidence intervals. We excluded the trial of flupentixol because its inclusion criterion was not specifically a diagnosis of borderline personality disorder.

Third, NICE guidelines are developed as a practical synthesis of clinical recommendations based on a pragmatic analysis of the evidence for the clinical effectiveness and cost-effectiveness, including evidence of harm, of particular treatments and approaches to a problem. As far as possible we do not rest NICE guideline development on speculative theory. The American Psychiatric Association based their recommendations about selective serotonin reuptake inhibitors and low-dose antipsychotics on a speculative theoretical model which has never been tested in hypothesis-driven studies. Treatment recommendations thus derived are based on post hoc reconstructions rather than primary evidence. Lieb et al implicitly use this model to understand the evidence and to develop recommendations.

Fourth, Lieb et al made recommendations regarding a number of drugs on the basis of single trials in which positive findings are restricted to one or two symptoms. They place greater emphasis on simple statistical significance without sufficient consideration of clinical significance, whether the outcome measures used were appropriate – in many cases they are not – or indeed the potential for harm. For example, valproate semisodium is an especially dangerous drug for women of child-bearing years who may unexpectedly become pregnant; and antipsychotics have a wide range of neurological side-effects, some of which can be permanent, as well as metabolic effects leading to weight gain and an increased risk of diabetes.

Finally, the NICE guideline considered evidence for non-drug treatments, for example psychological therapies, and looked at the care pathway within the National Health Service (NHS) in England and Wales. Recommendations relating to drug treatment were therefore developed in the context of evidence for the whole range of treatments for, as well as the clinical management of, borderline personality disorder. Consensus-based recommendations for the management of crises and sleep problems, experiences which in the NHS commonly lead to excessive reliance on various pharmacological solutions, were also included.

No drug has been licensed in the UK for borderline personality disorder. It is important that drugs that are used commonly within the NHS are subject to post-licensing surveillance by the Medicines and Healthcare products Regulatory Agency. It is therefore unusual for a NICE guideline to recommend the use of any unlicensed drug. There are exceptions to this, for example where there are no other treatments or other treatments are associated with significant harm. These remain exceptions, nevertheless. We hope that readers can see that, with these considerations in mind, the guideline group was correct in deciding not to recommend drug treatments for either the core symptoms of borderline personality disorder or indeed for any symptom clusters. More good-quality evidence is required.

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Lithium in drinking water

In their short report, Ohgami et al\(^1\) reported lithium levels in drinking water and linked them to the risk of suicide. Despite the report highlighting the pitfalls of drawing simple conclusions from large-scale ecological studies, a Google search shows that these findings have been widely disseminated in scientific and lay media.

A major concern, addressed only obliquely by the authors, is the likelihood of confounding in this scenario. As noted by Chandra & Babu,\(^2\) sociological factors play an important role in suicide.

The lack of accounting for such potential confounders for the different districts in the study is a serious methodological omission, rendering the results of the study untenable from an epidemiological perspective. The demographics of the different areas (beyond age structure) are not addressed, thus ignoring important economic and social factors (like deprivation and unemployment) which contribute to suicide risk.

Adjusting for differences in age structures between centres using standardised mortality ratios (SMRs) is unlikely to account for all important sources of confounding, so that the possibility of residual confounding must be considered a major qualifier when considering these results, rather than details to be addressed in future studies.\(^3\)

The potential reasons behind the difference in lithium levels in the drinking water samples in the different municipalities are also not explained. Lithium levels in water sampled across a number of districts in New Zealand differ within municipal areas, depending where the sample is sourced. In this context, how valid is it then to use the mean value to represent the lithium exposure in that area? This would require the matching of lithium levels with suicide data from each discrete area of water supply and a loss of statistical power for such a relatively uncommon event as suicide.

The duration of exposure to a specific level of lithium in the drinking water was also not addressed. Apart from the issue of dietary intake of lithium noted in the letter by Desai & Chaturvedi,\(^4\) there is the question of where people source most of their drinking water, and the use of bottled water.

In the context of the short report, it is also difficult to fully assess the suitability of the analysis methods used. It would have been useful to have more detail on the weighting structure used in the regression, alongside frequency data on the number of districts in New Zealand differ within municipal areas, depending where the sample is sourced. Also, the reported beta coefficient from the regression is not interpretable in the context of the presented figure or reported analysis methods.

Although the reported results were indeed intriguing, in the absence of more a developed approach to the research question it seems too early, and indeed misleading for a non-scientist audience, to even start speculating on the relationship between suicide rates and lithium in drinking water sources on the basis of these data. In this era of rapid information dissemination, the publishing of reports without rigorous scrutiny of the statistical method and due consideration of the confounding variables is a concern.


In 1990 we reported that the mean suicide rates in 27 Texas counties over a 10-year period were consistently lower in those with 'high' natural lithium content in the drinking water (70–160 mg/l) than in counties with 'medium' (12–60 mg/l) or 'low' (0–10 mg/l) water lithium levels.\(^1\) Ohgami et al\(^2\) have since argued, without proof, that these associations may have been spurious owing to what they considered an arbitrary division of the data. It is necessary, therefore, to emphasise that the data were partitioned in accord with accepted methods of statistical trend analysis and not in an arbitrary fashion, and that tests were conducted to assure that the partitioning of the data did not produce spurious associations.

Within the same study,\(^1\) we found the rates of homicide, rape, robbery, burglary and theft to be also lower in the high-lithium counties. In addition, a statistically significant reciprocal relationship between the water lithium levels and the arrest rates for possession of opium, cocaine and their derivatives was observed, while the arrest rates for lesser crimes such as possession of marijuana, drunkenness and driving under the influence showed no consistent dependence on the water lithium levels. The studies were later extended to include arrest rates of juveniles, yielding statistically significant results for possession of narcotic drugs and, interestingly, 'runaway from home'.\(^3\)

In the interest of historical accuracy it needs to be pointed out that in 1972 Dawson et al\(^4\) reported mental hospital admissions and homicide rates to be lower in high-lithium Texas counties. They also found the suicide rates to be lower in these counties, but the differences did not reach statistical significance, as incidence data for only a 2-year period (1968–1969) were compared.

Thus, the evidence in favour of beneficial effects of low levels of lithium on human behaviour is already strong, and since lithium is close to be officially recognised as a nutritionally essential trace element,\(^5\) emphasis should be placed on assuring adequate lithium intakes in populations at risk of developing lithium deficiency.


Authors’ reply: First, Drs Huthwaite & Stanley point out that a major concern is the likelihood of confounding in this scenario. In our previous research,\(^1\) we examined government statistics on suicide in the 47 prefectures in Japan. The overall yearly suicide rate in Japan was 25 per 100 000 population in 1999. Pearson’s correlation was used to calculate correlations of suicide rate with latitude, longitude, yearly mean temperature, yearly total sunshine, yearly mean individual income, and yearly unemployment rate in the 47 prefectures, although lithium levels were not measured in the study. There was a significant correlation with suicide rate for yearly total sunshine, yearly mean temperature, latitude, and yearly mean individual income. By using multiple regression analysis, yearly total sunshine was the only individual variable to predict significant variance in suicide rate. Taking these findings into consideration, we did not use yearly mean individual income or yearly unemployment rate.\(^2\) Also, yearly total sunshine was similar between the 18 municipalities of Oita prefecture so we did not use this. Most importantly, only 18 municipalities prevented us from conducting further analyses including confounding factors. We are now planning to perform a large study to consider confounding factors.

Second, they state that the potential reasons behind the difference in lithium levels in the drinking water samples in the different municipalities are also not explained and ask how valid it is then to use the mean value to represent the lithium exposure in that area. Lithium levels of drinking water supplies were measured at 26 locations in Oita city and at 53 locations in the other municipalities. The reason for the large difference in lithium levels is unknown, but Oita prefecture may have different geological features between the 18 municipalities and such differences may bring about large differences in lithium levels, although this thought is speculative. Also, instead of the mean value, we used the median value for the analysis and similar results were obtained.

Third, Huthwaite & Stanley question the duration of exposure to a specific level of lithium in the drinking water, and where people source most of their drinking water and the use of bottled water. In Japan, most people drink tap water although a small portion of people drink bottled water. Therefore, it is meaningful to measure lithium levels in tap water supplies. Moreover, the duration of exposure to a specific level of lithium is unknown, but if the residents continue to live at the same place, then their age may be associated with the duration.

Finally, we agree that in the context of the short report it is difficult to fully assess the suitability of the analysis methods used. Nonetheless, we emphasise that although short reports are not in themselves conclusive, they can provide new findings which lead to comprehensive research to establish a definite conclusion. We would like readers to read short reports with this in mind, so that they are not misled.

Although Schrauzer & Shrestha emphasise that their data were partitioned in accordance with accepted methods of statistical trend analysis, in their report\(^3\) they said only that the 27 Texas counties were classified into high, medium, and low groups according to the lithium content in the municipal water supplies. There was no explanation of how to divide the high (range 70–160 μg/l), medium (13–60 μg/l) and low (0–12 μg/l) groups. To avoid the suspicion of an arbitrary division, they should have fully described their method in their full paper. In addition, their results were adjusted only by population density and annual income.

Dawson et al\(^4\) also investigated suicide rates and lithium in drinking water, classifying lithium levels as high (≥70 μg/l) or low (<11 μg/l). This division might have derived from their previous study, in which they reported that the lithium levels were clustered into four groups (≤11, 11–29.9, 30.0–69.9 and ≥70 μg/l), which would provide about equal distribution of the measured values at consistent increments.\(^5\) Their results were adjusted by population density, the distance to the nearest state hospitals and rainfall.\(^6\)

Taking the nature of these partitions of lithium levels\(^3,5\) into consideration, our method of investigating the association between suicide rates and lithium in drinking water\(^7\) is more valid. We used lithium levels as a continuous variable and applied weighted least squares regression analysis adjusted for the size of each population. In any case, as Huthwaite & Stanley pointed out, confounding factors were not sufficiently investigated by Schrauzer & Shrestha\(^1\), Dawson et al\(^4\) or us.\(^2\) Therefore, beneficial effects of low levels of lithium on human behaviour has not been confirmed and further studies are clearly required.

References


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