COLLATED

July 20, 2017

Barry Blackwell: Risk and Relevance to Lithium Usage
Unpublished Letter to the Editor of JAMA

Collated by Olaf Fjetland

This collated document is comprised of Barry Blackwell's unpublished letter to JAMA, “Risk and Relevance to Lithium Usage,” posted on June 22, 2015, and the exchanges that followed its posting.

Three participants exchanged a total of four postings: two by Barry Blackwell and one posting each by Samuel Gershon and Gordon Johnson. The last entry in this exchange was made on August 29, 2015.

This collated document is now open to all INHN members for final comment.

Blackwell	June 25, 2015	essay
Gershon	July 2, 2015	comment
Johnson	August 13, 2015	comment
Blackwell	August 29, 2015	reply to Johnsons comment

Barry Blackwell: Risk and Relevance to Lithium Usage
Unpublished Letter to the Editor of JAMA

LETTER:

"As an octogenarian psychiatrist, previous author and occasional reader of JAMA, I enjoyed with irony two articles juxtaposed in the 2015 March 24/31 issue. In the Clinical Review and Education Section, Mark Olsen reviews work by Hampton et al. on '*Psychiatric Medication*

Adverse Events in Emergency room Visits ADE ED.' Among these are an estimated 16.4 per 10,000 outpatient visits (0.16%) due to lithium toxicity. Of these 'roughly one half' (53.6%) resulted in hospitalization, 0.08% of the total. This finding elicits the following comment from Olsen, 'The high frequency and clinical severity of adverse events associated with lithium should be considered amid calls to expand lithium treatment in bipolar disorders.'

"In 'JAMA Revisited' (p.1273), we find a reprinting of '*Why Physicians Err in Diagnosis'* (March 27, 1915), that identifies social and clinical errors, the former of which include what, at the time, were considered 'functional' psychiatric disorders, some that were probably treated with lithium, a panacea at that time.

"Today we recognize that lithium is the only naturally occurring, highly specific, remedy for a particular genetically based psychiatric condition, bipolar disorder, and that it is uniquely safe when adequately monitored by regular plasma levels. This is due to classical, but often overlooked work, by Trautner et al. (1955), which enabled Cade to rescind the ban he had placed on its use. (See Blackwell, B and others in *The Lithium Controversy: A Historical Biopsy* on INHN.Org in *Controversies,* June 19, 2014 and subsequent postings).

"It is a disservice to science, medicine and psychiatry to suggest that sloppy diagnosis or prescribing of a highly specific and effective remedy like lithium for a disabling disorder should become an excuse for limiting its appropriate use."

References

Blackwell, B in The Lithium Controversy: A Historical Autopsy. INHN.Org in *"Controversies."*

JAMA Revisited: Why Physicians Err in Diagnosis: 1915:64(13):1076, *JAMA,* 2015, 313(12).

Lee, M, Hampton *et al* Emergency Department Visits by Adults for Psychiatric Medication Adverse Events. *JAMA Psychiatry,* 2014, 71(9): 1006-1014.

M. Olsen. Surveillance of Adverse Psychiatric Medication Events.*JAMA*,2015,313(12)1273.

Trautner, EM, Morris, R, Noack, CH & Gershon, S. The Excretion and Retention of Ingested Lithium and its Effect on the Ionic Balance in Man. Med. J. Aust., 1955, 2: 280-291.

COMMENT ON LETTER:

The above "Letter to the Editor" of JAMA was duly submitted, meeting demands for fewer than 400 words and five references, an arduous process that severely taxed my geriatric computer skills. Several weeks later, I received a formal "Decision Letter" stating: "Considering

the opinion of our editorial staff we determined your letter did not receive a high enough priority rating for publication… we are only able to publish a small fraction of the letters submitted… which means that published letters must have an extremely high rating."

I was invited to "contact the author of the article although we cannot guarantee a response." This roused my professional ire. A scribe of authors (is this the correct collective noun?) delivered their verdict without seeking input from the reviewer or the original authors for comment on the validity of the concerns expressed.

The article on which the reviewer commented is an example of a massive data set that yielded statistically significant results of dubious clinical significance. The reviewer failed to address how to improve prescribing habits, but focused instead on alleged "over-prescribing" without any evidence or mention of how lithium treatment was managed, who the prescribers were (discipline and training) or any details of the patients' diagnosis, natural history or treatment responses.

A scribe of editors judged the reviewers conclusions and the author's study design did not merit seeking the opinion of either concerning issues raised by my letter. I could contact them myself but not expect an answer. This approach raises serious scientific and ethical concerns about editorial disinterest in the quality of what JAMA chooses to publish and how circling the editorial wagons stifles dissent.

The problem identified by this mega data is not new. It was reported 18 years ago by leading European psychopharmacologists (Kores and Lader, 1997), who studied 50 cases of severe lithium toxicity due usually to poor management.

My letter might have suggested a better, more practical solution to this problem compatible with the study design. Every patient admitted with side effects severe enough to warrant admission would be given, at the time of discharge, a brief (one page) outline of ideal management principles and advised to share it with their prescribing physician at a first outpatient visit. This might improve the physician-patient alliance, hopefully viewed by the doctor as prophylaxis for reduced risk of future malpractice litigation.

Of course such a suggestion might have increased the scribes "priority rating" although adding a sixth reference could have resulted in even more peremptory unthinking rejection.

Reference

Kores B. Lader MH. Irreversible Lithium Toxicity: An Overview. Clinical Neuropharmacology 1997; 20, 283-299.

June 25, 2015

Samuel Gershon's comment

Dr. Blackwell's letter and the response from JAMA provide us with some insights, both on clinical usage and the attitude of journal editors in this competitive age of scientific publishing, that is, the journal's interests are often directed to using pages to attain maximum impact factor scores. The author, Dr. Blackwell, was trying to present information that would not earn him the Nobel prize, but was to educate many psychiatrists of important practical issues about the use and management of lithium 65 years after its introduction with which many trainees and practitioners are not aware. This I think has created this apparent conflict.

July 2, 2015

Gordon Johnson's comment

The report on serious treatment emergent adverse effects with lithium in JAMA with over 50% *requiring hospitalisation is a wakeup call on the clinical practice of lithium usage. Adequate* monitoring including plasma levels has been rightly emphasised by Blackwell. Optimum plasma levels for maintenance of bipolar disorder balancing effectiveness and tolerability vary, but can be achieved for the majority of patients with levels of 0.6-0.8 mEq/L. This can be adjusted: bear in mind that levels above 0.8 increase the risk of adverse effects. Level of 1.0 mEq/L or above require review of risk/benefit. Levels below O.6 mEq/L may be less effective.

Adverse effects during maintenance may be insidious, but symptoms that should alert the clinician to impending intoxication are progressive weakness, difficulty in thinking and concentration, increased tremor, unsteadiness, and an increased thirst. Lithium intoxication can

occur with plasma levels within the therapeutic range emphasising the importance of clinical monitoring as well.

The frequency of plasma monitoring will depend on mood stability, compliance, potential drug interactions, older age with decreasing renal function and reduced lithium excretion, with dosage adjustment and adverse effects. Routine frequency of plasma monitoring would range from each 3-6 months. Plasma levels should be standardised, taken in the morning 12-14 hours after the last dose in the evening.

Lithium remains the first line treatment for maintenance in patients with bipolar disorder. Safety issues arise when appropriate clinical and plasma monitoring is ignored. This is an educational and training issue, not confined to the USA that has an impact on the use of lithium by the clinician and acceptance by the patient

August 13, 2015

Barry Blackwell's reply to Gordon Johnson's comment

Gordon Johnson's comments are affirmative and informative, correctly identified as "an educational and training issue," and coupled with wise and detailed advice culled from long experience.

How to disseminate this kind of advice to those who prescribe lithium but do not follow such guidelines, including primary care practitioners and specialists as well as psychiatrists, is a dilemma. It underlines concern that a prestigious, widely read journal, such as *JAMA* could overlook this aspect to focus instead on an unsubstantiated claim of "over prescribing." Lithium is highly effective, specific and cost effective for a disruptive disorder that can ruin and sometimes end the lives of its often highly productive victims.

An attempt to question the accuracy of the Journal's conclusion was never shared with their author, but received a cavalier dismissal from a group of sub-editors who voted it "lacked significance." One might conclude they were more concerned with protecting their pharmaceutical advertising revenue and the scientific integrity of a published but flawed conclusion.

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