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Should We Prescribe Lithium More Often?

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INTRODUCTION

Among the pharmacological drugs used in psychiatry, lithium is the oldest drug still being used regularly. After its initial use by the Danish neurologist Lange in the nineteenth century and its subsequent (re)discovery by the Australian psychiatrist Cade in 1949, the efficacy of lithium in the long-term treatment of bipolar disorder was finally established by Schou and his Danish colleagues in the 1960ies which led to its registration in Europe and the US as well as many other countries in the 1970ies (1). Nowadays, lithium is considered in many guidelines as one of the major options, if not the first choice in the long-term maintenance treatment of bipolar disorder. Nevertheless, it is not being used as frequently as what one would expect based on its place in these guidelines. In most countries, several other drugs which have become available as alternatives, i.e. the anticonvulsants carbamazepine, valproate and lamotrigine and several atypical antipsychotics which all are also registered for the long-term treatment of bipolar disorder, are being used more frequently. This despite the fact that in most guidelines they are not recommended as (single) first option, but only as one of the (first) options or even as second or third option.

What are the reasons for this apparent discrepancy?

It cannot be the lack of good efficacy data, as especially in recent years a new study and two meta-analyses have unequivocally shown that lithium is efficacious. In 2011, the so far largest study on the efficacy of lithium in the maintenance treatment of bipolar disorder was published (2). In this double-blind trial, bipolar I patients who had responded to and had tolerated quetiapine were randomized to continue with quetiapine or to switch to lithium or placebo. The results showed that both quetiapine and lithium were more effective than placebo in the prevention of any mood episodes, manic episodes and depressive episodes. Quetiapine was also more effective than lithium in the prevention of any mood episodes and depressive episodes, but this result should be interpreted with caution as the study design was enriched for quetiapine (see above) but not for lithium. The two recent meta-analyses, in which the Weisler study was included, confirmed the efficacy of lithium when concluding that "with no other drug available having such ample and consistent evidence for its efficacy, lithium remains the most valuable treatment option in this indication" (3) and that 'lithium seems to be the most reasonable candidate for

a first-line option for the long-term treatment of bipolar disorder' (4).

Another benefit of lithium is its anti-suicidal effect, which appears to be at least partially independent of its mood stabilizing effect as lithium may also decrease aggression and impulsivity. In a recent review with data from RCTs as well as naturalistic cohort studies Lewitzka et al. (5) concluded that "compelling evidence provides strong support that lithium has a suicide protective effect over the long-term course in patients with mood disorders." Its anti-suicidal effect in bipolar disorder was further supported in a recent Finnish nationwide registry-based study among bipolar patients hospitalized because of a suicide attempt between 1996 and 2003 (n=826) (6). The authors looked whether medication use was associated with hospitalization due to attempted suicides, deaths from suicide, and overall mortality during follow-up. Compared to no use, the use of lithium was associated with a (non-significantly) lower risk of suicide attempts, and with significantly decreased suicide mortality (RR=0.39, 95% CI=0.17-0.93, p=0.03) while the use of valproic acid (RR=1.53, 95% CI=1.26-1.85, p<0.001), antidepressants (RR=1.49, 95% CI=1.23-1.8, p<0.001) and benzodiazepines (RR=1.49, 95% CI=1.23-1.80, p<0.001) were all associated with an increased risk of attempted suicide and the use of antipsychotics did not reach statistical significance. This illustrates that lithium, despite its small therapeutic window and associated risks of an overdose, can be safely prescribed, if not should be seriously considered in suicidal bipolar patients.

If the well-established benefits of lithium are not the reason for its relative low use, it may be its potential harms. Lithium can lead to many adverse effects, of which especially its renal effect is considered a major harm. One of the major limitations of the above (and all other) meta-analyses is that while they looked at not only efficacy but also tolerability and overall satisfaction, their scope was never more than two years. However, when choosing a drug for long-term, if not life-long treatment, one should look at efficacy and safety not only during the first years of its use but also thereafter. While the use of lithium over more than 10 years is associated with the risk of chronic kidney dysfunction (CKD), the long-term use of atypical antipsychotics (as its major alternatives) is associated with metabolic syndrome and an increased mortality risk due to cardiovascular problems. Although it has not yet been established how these late adverse effects have an impact on the long-term safety of lithium and the atypical antipsychotics, the assumption is that also over a period of 10 or more years the safety of lithium is at least in balance with that of most atypical antipsychotics. However, it would be interesting to see studies in patients with bipolar disorder looking at mortality during treatment with lithium and its alternatives over more than 10 years, as has already been done with clozapine versus other antipsychotics in patients with schizophrenia (7).

What The Recent Studies have Indicated?

Three recent studies shed new light on lithium's potential harms. The first study (8) was a nationwide population-based study in Denmark, one of the countries with traditionally a relative high use of lithium, although lithium is no longer the most frequently prescribed drug in patients with bipolar disorder in Denmark (9). The study aimed to compare rates of CKD and in particular rates of end-stage CKD among individuals exposed to successive prescriptions of lithium, anticonvulsants, or other drugs used for bipolar disorder. Two cohorts were compared: cohort 1 comprised a randomly selected sample of 1.5 million individuals among all persons who were registered in Denmark in 1995, all patients with a diagnosis of a single manic episode or bipolar disorder between 1994 and 2012 (n=10.591), and all patients exposed to either lithium (n=26.731) or anticonvulsants (n=420.959). Cohort 2 included only the subgroup of 10.591 patients diagnosed as having bipolar disorder.

In cohort 1, 0.8%, 1.0%, and 0.2% and in cohort 2 and 2.6%, 3.0%, and 0.6% were diagnosed as having possible, definite, or end-stage CKD, respectively. Based on the total sample and not considering diagnoses (cohort 1), use of lithium was associated with an increased rate of definite CKD (0 prescriptions:

hazard ratio [HR]=1.09, 95% CI=0.81-1.45; ≥60 prescriptions: HR=3.65, 95% CI=2.64-5.05; p for trend < 0.001) and possible CKD (0 prescriptions: HR=1.01, 95% CI=0.79-1.30; ≥60 prescriptions: HR=2.88, 95% CI=2.17-3.81; p for trend <0 .001), whereas use of anticonvulsants, antipsychotics, or antidepressants were not. Remarkably, neither use of lithium nor use of any other drug class was associated with increasing rates of end-stage CKD.

In patients with bipolar disorder (cohort 2), use of lithium was also associated with an increased rate of definite CKD (1-2 prescriptions: HR=0.89, 95% CI=0.39-2.06; ≥60 prescriptions: HR=2.54, 95% CI=1.81-3.57; p for trend <0.001) or possible CKD (1-2 prescriptions: HR=1.26, 95% CI=0.65-2.43; ≥60 prescriptions, HR=2.48, 95% CI=1.80-3.42; p for trend <0.001). Surprisingly, the use of anticonvulsants was also associated with definite CKD (1-2 prescriptions: HR=1.23, 95% CI=0.76-1.99; ≥60 prescriptions, HR=2.30, 95% CI=1.53-3.44; p for trend <0 .001) and with possible CKD (1-2 prescriptions: HR=1.11, 95% CI=0.70-1.76; ≥60 prescriptions: HR=1.97, 95% CI=1.34-2.90; p for trend <0.001). There was no such association with antipsychotics or antidepressants. Also in patients with bipolar disorder, use of lithium was not significantly associated with an increased rate of end-stage CKD, whereas use of anticonvulsants was (1-2 prescriptions, HR=0 [95% CI, 0.00-infinity]; 30-39 prescriptions: HR=3.23, 95% CI=1.26-8.27; ≥60 prescriptions: HR=2.06, 95% CI=0.82-5.16; p for trend=0.002). This latter finding of increased CKD among patients using anticonvulsants may be explained by selective prescription of these drugs to patients with already existing CKD, including patients with prior lithium use who had developed CKD. Nevertheless, the authors conclude: "Maintenance treatment with lithium or anticonvulsants as practiced in modern care [WN: i.e. with regularly monitoring of kidney function and lithium plasma levels] is associated with an increased rate of CKD. However, use of lithium is not associated with an increased rate of end-stage CKD."

In the second study looking at laboratory data from the Oxford region (UK) Shine et al. (10) investigated the incidence of renal, thyroid, and parathyroid dysfunction in patients (aged ≥18 years) having used lithium and who had at least two creatinine, thyrotropin, calcium, glycated hemoglobin, or lithium measurements between 1982 and 2014 (n=2.759), compared with controls who did not have lithium measurements taken (n=689.229). Lithium use was associated with an increased risk of stage three CKD (HR=1.93, 95% CI=1.76-2.12; p<0.0001). Furthermore, lithium use was associated with hypothyroidism (2.31, 2.05-2.60; p<0.0001) and raised total serum calcium concentration (1.43, 1.21-1.69; p<0.0001), but not with hyperthyroidism (1.22, 0.96-1.55; p=0.1010) or raised adjusted calcium concentration (1.08, 0.88-1.34; p=0.4602). The adverse effects occurred early in treatment (HR<1 for length of treatment with lithium), possibly biased by stopping lithium in patients who developed the adverse event. Higher than median lithium concentrations were associated with increased risk of all adverse outcomes. Also this study shows that use of lithium is definitely associated with severe adverse effects, but fortunately very severe outcomes such as end stage CKD or increased mortality do not appear to be increased.

Lithium Intoxication

A final serious problem associated with the use of lithium is the risk of lithium intoxication, which can be the result of a deliberate overdose as suicide attempt, but also the result of a chronic intoxication, e.g. to insufficient water (and salt) intake or concomitant use of other drugs lowering the excretion of lithium and thus leading to increased lithium plasma levels (11,12). Although lithium intoxications can be serious and can lead to serious and lasting damage, such as a cerebellar syndrome, it can be prevented by extensive psychoeducation, the use of a warning system in monitoring the prescription of concomitant drugs, and last but not least by frequent monitoring of not only lithium plasma levels, but also kidney function (creatinine), thyroid function (T4 and TSH), and parathyroid parameters.

CONCLUSION

Given its excellent efficacy and despite its potential adverse effects, lithium should be considered as the first choice in every patient with bipolar disorder with an indication for maintenance treatment (13). Furthermore, its use requires experienced doctors, and in my opinion treatment of our bipolar patients preferentially in centers specialized in the treatment of bipolar patients with lithium.

Potential Conflicts of Interest

During the years 2011-2016 W.A. Nolen has received grants from the Netherlands Organization for Health Research and Development, the European Union; has received honoraria/speaker's fees from Astra Zeneca, Lundbeck; and has served as consultant for Daleco Pharma.

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