Improving the appropriateness of depression treatment in patients with advanced chronic kidney disease

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With regard to recent evidence, we fully appreciate the call by Walter and collaborators for the psychiatry and nephrology communities to conjointly address the issue of treating depression in patients with advanced chronic kidney disease (CKD) [1]. Considering that one-quarter of US adults with CKD may be affected by depression (i.e. about 7 million US adults) [2], the issue of depression in patients with CKD (on or not on dialysis) appears to be a crucial far-reaching concern in both nephrology and psychiatry. Furthermore, in clinical practice, we are all aware of difficulties in the management of comorbidities in patients with severe chronic disease. Unfortunately, patients with depressive episodes and patients with CKD and end-stage renal disease (ESRD) are not immune to this complex reality. We feel confident that more holistic and multidisciplinary approaches will help obtain breakthroughs in diagnosis and treatment.

Hedayati and colleagues elegantly reported a recent adequately-powered study targeting antidepressant therapeutic strategies for patients with major depressive disorder and CKD (not on dialysis) [3]. The study found no expected improvement in depression in the sertraline group (vs. the placebo group). Similar negligible differences were found between placebo and sertraline arms following a randomized controlled trial over 6 months in patients on hemodialysis with major depressive disorder [4]. Nonetheless, the efficacy and safety of pharmacological therapies for the treatment of depression among CKD and ESRD warrant further investigation and presumably the creation of other solutions.

This issue is of prime importance; only one-third of depressed patients achieved clinical remission after the first

antidepressant trial, with 30–40% of patients being classified as non-responders to first-line treatments at adequate dose and duration [5]. Clearly, tolerability has improved, yet 85% of patients under selective serotonin reuptake inhibitors experience at least one side effect during the early stages of treatment. Assuming that patients with chronic illness and multiple comorbidities (including depression) are more likely to demonstrate a response failure to the first antidepressant treatment, alternative therapeutic approaches could be appropriate.

Without rejecting the pharmacological approach, a possible treatment for depression in patients with CKD or ESRD may be the use of repetitive transcranial magnetic stimulation (rTMS). As reported by a group of European experts commissioned by the European Chapter of the International Federation of Clinical Neurophysiology, there is now sufficient evidence to support the efficacy of rTMS (level A: “definitely effective”) protocols in depression [6]. Admittedly, no studies have addressed the safety concerns in depressed patients with CKD. Nonetheless, the safety profile of these non-invasive brain stimulation techniques appears very high for many clinical indications (e.g. pain, epilepsy, schizophrenia, craving, or addiction) [6]. This alternative will offer the opportunity to overcome several barriers to treatment of depressed patients with CKD/ESRD, particularly since almost half of these patients do not want treatment for their depression because of the already high medication burden [7], and considering that some psychotropics (e.g. lithium) may be contraindicated for patients with CKD [8].

To confirm the antidepressant efficacy of rTMS, some background of well-known theoretical guidelines and action mechanisms is certainly worth a review. Quite simply, rTMS is a safe, non-invasive method involving the placement of an electromagnetic coil on the scalp that facilitates a relatively painless stimulation of the brain cortex by inducing electric currents (pulses) in trains of repetitive stimuli at an appropriate frequency and intensity (110% of active motor

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threshold). Empirically, excitatory high-frequency stimulation (≥ 5 –20 Hz) of the left dorsolateral prefrontal cortex or inhibitory low-frequency stimulation (≤ 1 Hz) of the right dorsolateral prefrontal cortex can be used for a minimum of 4 weeks (5 sessions per week; 1200 pulses per session) as an efficient treatment for resistant major depression. While modifying cortical excitability, rTMS generally promotes the dopamine release in striatal-projection pathways and feedback loops with the prefrontal cortex in the hypothalamic-pituitary axis, which compensates for the depression-related hypercortisolemia. Still, the effects of frontal rTMS are not only local, but are also accompanied by changes in the functional connectivity between deep brain structures (striatum, thalamus, and anterior cingulate cortex) involved in mood regulation and the pathophysiology of depression; a better rTMS-induced regulation of activity in the frontal and limbic areas (respectively, hypoactive and hyperactive in depressive and anxiety disorders) is associated with the recovery of the frontostriatal and fronto-insular functional connectivity.

According to recent meta-analyses addressing the efficacy of rTMS in treating clinical depression and/or drug-resistant major depression (i.e. at least two episodes of depression that have been resistant to antidepressants after 6 weeks of treatment) in the general population, all of the included placebo-controlled trials confirm the significant improvement of depressive symptoms after an rTMS treatment (which is approximately twice as effective as a sham procedure), with remission rates of 35% on average [9]. It is worth noting that no meta-analysis has focused on the antidepressant efficacy of rTMS for no-drug resistant depression, *a fortiori* in patients with CKD or ESRD. However, the risk of intolerance to psychotropics in those vulnerable patients (often already on multiple medications) should make rTMS a first-line treatment. Proof of rTMS' effectiveness for treating depression in adults with CKD and ESRD will likely have positive consequences. It will undoubtedly improve patients' mood, quality of life, and medical outcomes, including fewer emergency visits, hospitalizations, cardiovascular events, peritonitis, withdrawal from dialysis and suicide [10]. Given the very high prevalence of depression in patients with CKD and ESRD (around one-third) and the inconclusive evidence so far for pharmacological interventions, developing effective combined psychiatry-nephrology models of care for such patients is an attractive prospect for improving the screening and management of depression in routine CKD care. To this end, rTMS treatment provides an encouraging option.

To our knowledge, only one study tested the (proteinuric) effect of rTMS in diabetic patients with stage 3–4 CKD; no side effects were reported during and after the rTMS procedure, confirming the feasibility of large randomized placebo-controlled studies to test the beneficial effects of rTMS

on depression in CKD. In the same vein, a second possible non-invasive neuromodulation treatment is the use of transcranial direct current stimulation (tDCS) for which level B ("probably effective") evidence was found for depression [11]. Interestingly, its use for treating depression in eight hemodialysis patients has been tested [12], with promising positive results, despite the too small sample size. Additionally, the tDCS devices whose easy management and low cost allow at-home use by the patient (and *a fortiori* in clinical settings) could also be combined with aerobic exercise programs, thereby enhancing the potential of antidepressant effectiveness of non-drug approaches.

A new frontier awaits for an effective clinical psychiatry-nephrology practice in neurostimulation.

Compliance with ethical standards

Conflict of interest The authors report no conflicts of interest.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

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