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Research article

Depression in chronic kidney disease: Particularities, specific mechanisms and therapeutic considerations, a narrative review

Antoine Lefrère [a,b], Stéphane Burtey [c,d], Stanislas Bobot [e], Raoul Belzeaux [f,g,h], Mickaël Bobot [c,d,i,*]

[a] Pôle de Psychiatrie, Assistance Publique Hôpitaux de Marseille, Marseille, France
[b] Institut de Neurosciences de la Timone, Aix-Marseille Univ, UMR CNRS, France
[c] Centre de Néphrologie et Transplantation Rénale, Hôpital de la Conception, AP-HM, Marseille, France
[d] Aix Marseille Univ, INSERM 1263, INRAE 1260, C2VN, Marseille, France
[e] Psychologie de la Santé, Université Toulouse Jean Jaurès, Toulouse, France
[f] IGF, Université de Montpellier, CNRS, INSERM, Montpellier, France
[g] CHU Montpellier, Department of psychiatry, Université~ de Montpellier, CNRS, INSERM, Montpellier, France
[h] Fondation Fondamental, Créteil F-94010, France
[i] CERIMED, Aix-Marseille Univ, Marseille, France

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ABSTRACT

Introduction: Depression is highly prevalent during chronic kidney disease (CKD) with studies suggesting prevalence rates ranging from approximately one-quarter to half of CKD patients. CKD and depression have a bidirectional relationship, each disorder aggravating the other, leading to more complex and challenging patient management. Depression during CKD is multifactorial and is associated with increased risk of adverse events and hospitalization.

Methods: We conducted a narrative review of experimental and observational studies in animals and humans, as well as meta-analyses, to explore specific mechanisms of depression in CKD and its treatment.

Results: In depression the gut-brain axis is central. CKD leads to an accumulation of gut-derived uremic toxins. One key factor is the accumulation of tryptophan-derived uremic toxins like kynurenines or indoxyl sulfate, whose serum concentration increases progressively with the stage of CKD (up to 100-fold in stage 5), and which plays an important role in depression mechanisms, by activating aryl hydrocarbon receptor, decreasing brain concentrations of serotonin by approximately 40 %, increasing brain inflammation, via activation of microglia and astrocytes and release of TNFα, IL-6 and NO. Randomized controlled studies found limited or no benefits of antidepressants for depressive symptoms in CKD and hemodialysis patients.

Conclusion: Chronic inflammation, in relation to uremic toxin accumulation during CKD, seems to be a complex but important mechanism for treatment resistance in depression. Future research should consider inhibitors of uremic toxins inhibitors and anti-inflammatory molecules as potential therapeutic agents, to improve the prognosis of depression in CKD patients.

1. Introduction

Depression is a common psychiatric disorder and one of the leading causes of disability worldwide. According to the World Health Organization, depression affects approximately 5 % of adults in the general population, with higher rates observed in women (6 %) compared to men (4 %) [1]. Among patients with chronic kidney disease (CKD), depression is even more prevalent and represents the most common psychiatric disorder)[2]. Meta-analyses and broader studies consistently report a notably high prevalence of depression among CKD patients, with about one-quarter of all CKD patients exhibiting clinically significant depression—a rate considerably higher than that observed in the general population[3–5]. Furthermore, a recent study on 103 participants revealed that more than half experienced depression and anxiety, with prevalence rates of 58.3 % and 50.5 %, respectively. In this study, these depressive symptoms were clearly associated with lower quality of

* Correspondence to: Service de Néphrologie et Transplantation Rénale, 147 boulevard Baille, Marseille 13005, France.
E-mail address: mickael.bobot@ap-hm.fr (M. Bobot).

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life domain scores[4]. Additionally, the prevalence of depression in CKD patients increases with the stage of CKD, reaching up to 73 % in end-stage kidney disease (ESKD)[6].

The interaction between these conditions reveals a complex, bidirectional reinforcing relationship where each disease contributes to exacerbating the severity and progression of the other, thereby complicating patient management. Depression is more prevalent in patients with chronic illnesses, complicating their management and contributing to poor treatment adherence, higher hospitalization, and mortality rates[7,8]. CKD is not an exception; depression in CKD is also associated with increased mortality and hospitalization rates, reduced treatment compliance, and diminished quality of life[9,10].

Emerging evidence highlights the critical role of uremic toxins, particularly tryptophan-derived metabolites such as indoxyl sulfate, in the pathophysiology of depression during CKD. These toxins accumulate as kidney function declines and are believed to contribute to depression through mechanisms such as activation of the aryl hydrocarbon receptor (AhR), decreased serotonin levels in the brain, and increased neuroinflammation. Addressing these mechanisms could offer new therapeutic pathways to mitigate the bidirectional relationship between depression and CKD.

In this review, we explore the complexities of depression in CKD, focusing on the clinical challenges and emerging insights into potential therapeutic strategies to improve outcomes for these patients.

2. Clinical Presentation and diagnostic challenges of depression in CKD

Depression, as defined in DSM 5, is characterized by depressive mood and/or anhedonia, accompanied by symptoms such as sleep and appetite disturbances, psychomotor changes, fatigue, sense of worthlessness, cognitive disturbances, and recurrent thoughts of death or suicide ideation[11]. These symptoms must persist for at least 2 weeks and cause significant functional impairment. While the diagnostic criteria are clear, the lack of biomarkers makes diagnosis reliant on clinical evaluation which poses challenges, especially in CKD patients.

In CKD, overlapping symptoms like fatigue, sleep disturbances, sexual dysfunction, and cognitive impairment complicate the differentiation between depressive and CKD-related symptoms[12]. Reliance on self-reported questionnaires such as the Beck Depression Inventory (BDI)[4,13,14]), including low or mild intensity (e.g., BDI-II $\geq$ 11[4,13,14]), which could lead to diagnosing depression based on non-specific symptoms such as sadness, fatigue, and lack of energy. These symptoms might also be direct consequences of CKD and its comorbidities (e.g., anemia).

Studies have also reported discordance between depression levels identified through self-reported tools and formal diagnostic evaluations [15].

To address these challenges, formal diagnostic interviews, such as the Structured Clinical Interview for DSM Disorders (SCID) or the Mini-International Neuropsychiatric Interview (MINI), are recommended to distinguish depressive symptoms from somatic manifestations of CKD [16]. Incorporating CKD-specific patient-reported measures and fostering collaboration between nephrology and psychiatry can further refine diagnostic accuracy. These steps pave the way for early detection and integrated care models that address the biological and psychosocial complexities of depression in CKD patients.

3. Psychological aspects

Chronic diseases profoundly affect patients' quality of life due to their prolonged and progressive nature, entailing significant physical and psychological challenges. The diagnosis of a chronic illness can be experienced as an emotional shock, leading to a grieving process for patients, and often resulting in feelings of despair and anxiety. The day-to-day management of chronic illness, often involving a strict diet, medication and frequent medical appointments, can generate considerable stress. The accumulation of these emotions, combined with feelings of being overwhelmed by the demands of treatment and the physical symptoms of the disease and functional limitations, can aggravate symptoms of depression. Conversely, depression can intensify negative perceptions of chronic illness symptoms, creating a vicious circle[17].

Patients' perceptions of CKD vary widely and are influenced by various factors that influence feelings of depression. Indeed, some patients, not experiencing symptoms, may underestimate the severity of the disease. On the other hand, those who do experience symptoms such as fatigue have a major impact on their daily lives. CKD also affects patients' family and social relationships, increasing feelings of isolation and dependence. Uncertainty about the progression of CKD and future treatments often generates anxiety and sadness. Moreover, patients' perceptions of the efficacy and side effects of treatments influence their adherence to medical recommendations. Patients generally feel better when they believe they have control over their disease, notably by adopting a healthy lifestyle and monitoring their health status[18]. On the other hand, severe depression is associated with poorer understanding of the disease[19]. ESKD also induced specific psychosocial challenges, such as financial constraints and inability to work due to dialysis[2]. Depression has also a negative impact on cognitive performance and its repercussions on activities of daily living. Indeed, longitudinal studies found that worsening depression in patients with mild cognitive impairment leads to a significant deterioration in their financial capacity over a one-year period (evaluated using the LCPLTAS scale), compared to patients with stable depression, patients with MCI without depression, and cognitively healthy individuals[20], emphasizing the importance of longitudinal monitoring of depressive symptoms in chronic diseases associated with cognitive impairment, such as CKD[21].

Perceptions of the general population regarding kidney diseases, particularly their perceived link to psychosocial factors such as stress and depression, can significantly influence treatment adherence, lifestyle choices, and the seeking of medical help. It has been shown that these perceptions, often influenced by misconceptions, affect patients' experiences in different sociocultural contexts. For example, a study conducted in Greece found that participants from the general population know little about kidney diseases, 60 % of them associated kidney diseases with depression and 75 % with stress[22]. It highlights the importance of educational initiatives: a better understanding of kidney diseases and their connection to psychosocial factors could reduce the stigma associated with them, encourage prevention, and promote more proactive care.

4. Factors associated with depression in CKD

Studies investigating factors associated with depression in CKD have identified several key elements. These factors include gender, education level, family support, financial support, employment status, CKD duration, income, social status, and social support[13,15,23]. Additionally, negative illness perception, low self-esteem, and severe pain interference have been linked to depression in CKD patients[13]. Lower educational attainment has also been associated with higher rates of major depression, likely due to reduced access to screening and treatment[15]. These factors likely contribute to depressive symptoms through mechanisms such as chronic stress, systemic inflammation, and reduced coping capacity. While these risk factors are well-documented, protective factors in CKD remain underexplored. However, general evidence suggests that strong social support, effective coping strategies [24], and lifestyle behaviors like regular exercise and a nutrient-rich diet could mitigate depression[25]. These factors may buffer stress, reduce inflammation, and improve emotional regulation, though their specific impact in CKD populations is not well-studied.

5. CKD as a risk factor for developing depression

Recent findings indicate that CKD patients, particularly those with reduced eGFR below 60 mL/min/1.73 m^2, have a higher risk of experiencing depression compared to individuals with normal kidney function (eGFR $\geq$ 90 mL/min per 1.73 m^2)[26].Data from the China Health and Retirement Longitudinal Study (CHARLS), supports this observation. The study found that lower baseline eGFR, both calculated from creatinine (eGFRcr) and cystatin C (eGFRcr-cys) were significantly associated with higher depression scores over a four-year follow-up period. Notably, the risk of depression increased concomitantly with declining kidney function, highlighting a dose-response association [27].

6. Depression as a risk factor for CKD

Conversely, depression may also act as a risk factor for the onset of CKD. Significant research including a large nationwide dataset suggested that individuals with depression have a 38 % higher risk of developing CKD compared to those without depression[26]. Longitudinal study found that depression was associated with a higher risk of rapid decline in eGFR, indicating that depressive symptoms are longitudinally associated with new-onset CKD, ESKD, and hospitalization due to acute kidney injury (AKI)[28].

7. Impact of depression on CKD outcomes

Research from the Stockholm CREAtinine Measurements (SCREAM) project involving 157,398 adults with CKD stages 3–5 not on dialysis shows that depression is significantly associated with adverse CKD outcomes. Over a median follow-up of 5.1 years, 8.1 % of patients developed depression, which was associated with a 38 % increased risk of CKD progression (HR: 1.38, 95 % CI: 1.28–1.48)[29]. Additionally, depression was linked to a higher risk of major adverse cardiovascular events (HR: 1.22, 95 % CI: 1.18–1.27) and all-cause mortality (HR: 1.41, 95 % CI: 1.37–1.45). These patients also experienced more hospitalizations (HR: 1.77, 95 % CI: 1.71–1.83), reflecting greater healthcare utilization. While these findings suggest a robust association between depression and CKD outcomes, they do not establish causality. Further studies, including prospective and interventional designs, are needed to elucidate causal pathways

8. Significant bidirectional relationships between depression and CKD

Recent studies have confirmed a significant bidirectional relationship between depression and CKD. In the Coronary Artery Risk Development in Young Adults (CARDIA) study, young and middle-aged adults with depressive symptoms had a 28 % higher risk of developing CKD [30]. Conversely, individuals with CKD showed a 36 % increased risk of developing depression during the follow-up period. This bidirectional relationship has been also observed in the China Health and Retirement Longitudinal Study (CHARLS), which found that baseline depression increased the likelihood of CKD by 38 %, while CKD increased the risk of subsequent depression by 48 %. These findings were consistent across various sensitivity and subgroup analyses[26].

These findings underscore the necessity for integrated care approaches, where routine screening and timely management of depressive symptoms in CKD patients, and vice versa, are prioritized. This comprehensive approach can potentially mitigate the progression of both conditions, improving clinical outcomes and enhancing the quality of life for affected individuals.

9. Biological aspects of depression in CKD

Pathophysiology of depression remains unclear although a considerable amount of works since the discovery and description of the monoamine hypothesis of depression. Today, depression is considered as a complex interplay between a vulnerable genetic background, unfavorable environment including childhood trauma and recent adverse life events. Epigenetic mechanisms may intervene in such interactions. Depression involves serotonin, noradrenalin and dopamine deregulation, mild to moderate peripheral inflammation. Beyond monoamine and functional alteration of brain activities, the central nervous system demonstrates pathology of glial cells (microglia activation, astrocyte dysfunction) and some brain structure alterations have been also described [31,32]. A complex crosstalk between immune systems and central nervous system has also been suggested [33].

Chronic low-grade inflammation is a cornerstone of the biological hypothesis of depression. Elevated cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP) interfere with neurotransmitter pathways, reduce synaptic plasticity, and foster neuroinflammation [34]. This inflammatory state can impair emotional processing and lead to persistent depressive symptoms. Notably, systemic inflammation has been shown to activate neuroinflammatory pathways, such as TLR-4/NF-κB and NLRP3 inflammasome signaling, which perpetuate immune responses in the brain. Anti-inflammatory interventions have demonstrated efficacy in alleviating depressive symptoms, further supporting inflammation's central role in mood disorders.

Disruptions in the microbiota-gut-brain axis, particularly in CKD, intensify systemic inflammation and contribute to mood dysregulation. Dysbiosis, characterized by reduced populations of beneficial bacteria like *Faecalibacterium* and increased intestinal permeability, elevates systemic inflammation and contributes to neuroinflammatory processes [35].Changes in microbiota composition influence neurotransmitter production, particularly serotonin, and alter brain function through microbial metabolites such as short-chain fatty acids. These effects establish a bidirectional relationship between gut health and mental well-being, with dysbiosis exacerbating both systemic inflammation and mood dysregulation [35].

In the context of CKD, these mechanisms could further be intensified by the accumulation of uremic toxins.

10. Role of the uremic toxins

The association between the severity of CKD and the prevalence of depression suggests a role of the solutes accumulating with the progression of CKD. These solutes are called uremic toxins. The uremic toxins are metabolites normally eliminated by the kidneys through glomerular filtration and tubular secretion, associated with biological and clinical effects[36].

One major family of uremic toxins are derived from tryptophan (Trp) [37]. Tryptophan is an essential amino acid in humans. Humans are dependent on dietary tryptophan to cover their needs, the recommend daily dose is 4–5 mg/kg. Only 1 % of the tryptophan is used for production of proteins, the majority is metabolized in five pathways [38], quantitatively (90 % of the Trp) the most important is the kynurenine pathway leading to the production of nicotinamide (NAD). The kynurenine metabolites are glutaminergic modulators, certainly playing a role in mood disorders[39]. Recently it was shown that a low kynurenic acid (KA) concentration in urine and a decreased KA / quinolinic acid ratio is associated with an increased severity of depression[40]. It is to note that Kynurenine pathway regulates inflammation, and it was suggested that inflammation could be an important mediator of severe depression.

The second (1–2 %) is the serotonin pathway leading to the production of serotonin and melatonin.

The third (4–6 %) is the indole pathway. Compared to the other pathways the metabolites are produced by the transformation of the Trp in the gut by tryptophanase into indole. The indole is then transformed mainly by the liver into various metabolites. The best known as uremic toxins is the indoxyl sulfate.

The two other pathways are less well known, one leads to the production of tryptamine and the last described to the production of indole pyruvic acid through the interleukin 4 induced-1 (IL4i1) enzyme. The tryptophan metabolic pathways are illustrated in Fig. 1.

The most studied tryptophan-derived uremic toxins (TDUT) are the kynurenines and indoxyl sulfate. The serotonin pathway is of high interest in depression. The production of serotonin in the brain of patients with CKD has not been studied previously. In platelet-poor plasma serotonin concentration increased with reduction of GFR [41]. But a substantial portion of patients with CKD have very low serum levels of serotonin and have the highest cardiovascular risk. On the other hand, a certain proportion of patients with high serotonin concentration exhibits an increased risk of cardiac events. Interestingly, the indoxyl sulfate induced a reduction in the brain production of serotonin by approximately 40 %[42,43]. This suggest that high indoxyl sulfate concentration, by reducing the brain concentration of serotonin, could play a major role in the depression. Accumulation of indoxyl sulfate in the blood lead to an activation of aryl hydrocarbon receptor (AhR) leading to behavioral comportments in rats and mice, in relation with increased blood-brain barrier (BBB) permeability suggesting that TDUT are major player in depression during CKD [44]. This was comforted by the association of proinflammatory microbiota with depression in patients with CKD [45]. In rats, accumulation of TDUT is associated with anxiety [46]. Indoxyl sulfate leads to brain inflammation[47], a classical mechanism of resistant depression, via activation of AhR and NFκB pathways. Exposure to high levels of IS increased astrocyte and microglial activation, and release of NO, IL-6 and TNFα by these cells[47]. It is of high interest to note that in non-CKD population the concentration of IS is associated with the severity of anxiety [48]. Then, studying uremic toxins could help to better understand the relation with so called gut-brain axis and depression.

The main receptor of kynurenine metabolites and indole metabolites is AhR. The activation of AhR by its canonical agonist the dioxin induce depression-like symptoms in mice suggesting that all the strong agonists of AhR like indoxyl sulfate or KA could induce depression [49]. In addition, inhibitors of AhR could act as antidepressants [50,51]

Beside TDUT, the modification of dopamine system observed in CKD could play a role in some manifestation of depression[52]. Also, paracresyl sulfate, a uremic toxin derived from phenylalanine, could play a role in depression [53]. Recently, a phenol metabolite 4-ethylphenyl sulfate (4EPS) from the family of paracresyl sulfate was reported to have an effect on the comportment of mice [54]. The Janus-faced effects of metabolites accumulated during CKD were described [55]. For example, a uremic toxin indole 3 propionic acid could improve social function in a mice model of 16p11.2 microdeletion[56]. Another example is the recent observation that reduced concentration of ammonia could increase depression in animal models but increased plasma concentration of ammonia could improve the stress[57]. To note, ammonia is increased in CKD, suggesting a mechanism of protection against accumulation of deleterious uremic toxins. We must keep in mind that some gut-derived metabolites could have beneficial effects, and we must have a more holistic approach to improve the understanding of the relation between kidney and brain.

The reduction of TDUT concentration could be a therapeutic approach to improve the care of depression. Many approaches were proposed to reduce the blood concentration of TDUT[58]. We must keep in mind that some pathways have redundancy. Recently it was shown that the inhibition of IDO in cancer did not improve the prognosis of

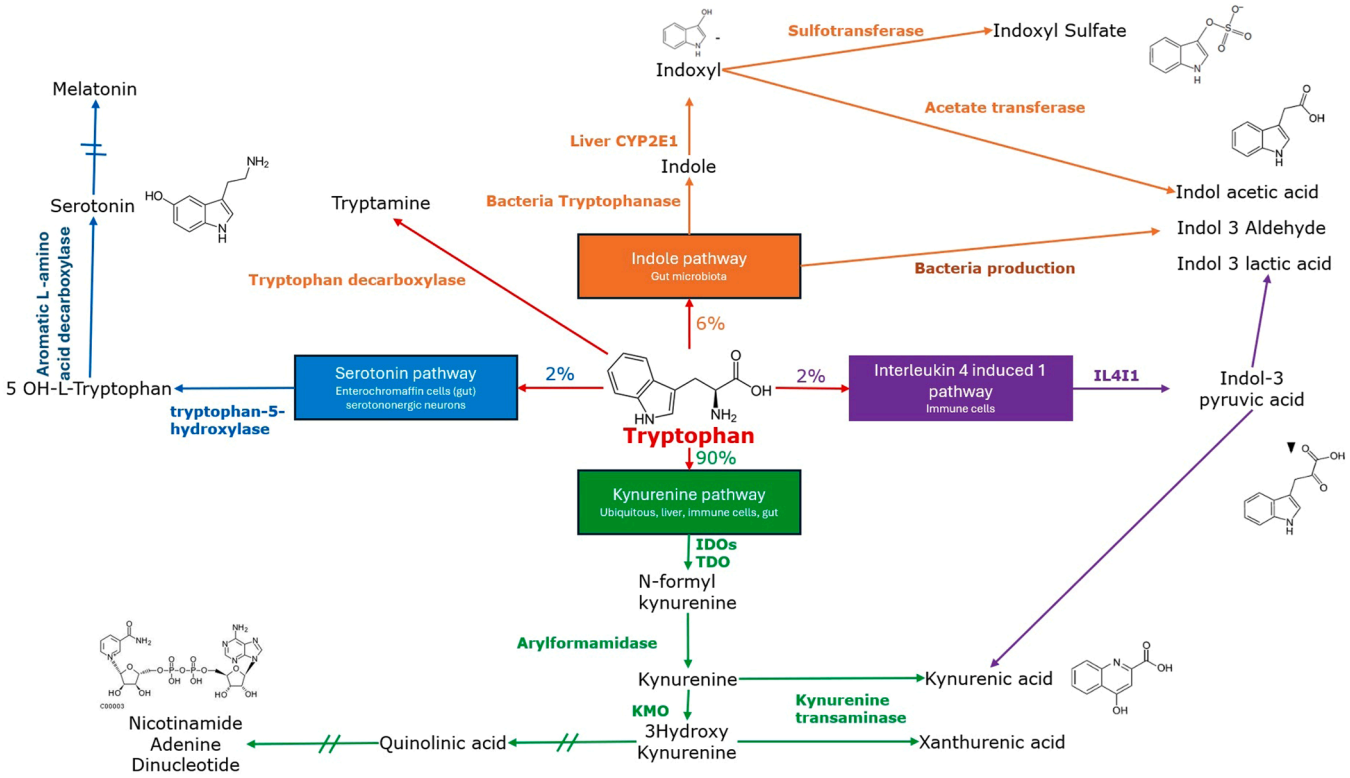

Fig. 1. Production of tryptophan metabolites. Tryptophan is an essential amino acid for humans. The minimal intake is 5 mg/kg/day. 90 % of the intake is used by the kynurenine pathway (IDO: indoleamine dioxygenase, TDO: tryptophan dioxygenase, KMO: kynurenine 3-monooxygenase) to produce kynurenine, kynurenic acid and xanthurenic acid, 3 main uremic toxins. The pathway leads to the production of NAD. 6 % of the ingested tryptophan is metabolized by the gut microbiota in the indole pathway. Bacteria produced directly many indole derivatives like Indol 3 lactic acid. Mostly, the tryptophanase of more than 80 bacterial species produces indole that is absorbed by the gut to be transformed by the liver mainly in indoxyl sulfate, a major uremic toxin. Recently a new pathway that could produce kynurenic acid was discovered, the Interleukin 4 induced 1 pathway. This pathway plays a major role in the production of indole in the context of cancer. Finally, 2 % of the tryptophan is metabolized in serotonin and melatonin. The last pathway is the production of tryptamine mainly by the gut after decarboxylation of tryptophan.

patients mainly because kynurenic acid is still produced by the IL4i1 pathway[59]. So, it is necessary to test the treatment in randomized clinical trials. The most evident way to reduce the concentration of indoxyl sulfate is to reduce the amount of tryptophan afford by diet. Low protein diet or Mediterranean diet reduce the concentration in total and free indoxyl sulfate[60]. The increased ingestion of fibers is also associated with reduction of IS[61]. So, the reduction of protein or increase of fibers in diet could be interesting to improve depression, this must be evaluated in interventional approaches. Another way to reduce TDUT could be the modification of the gut microbiota. It is efficient in preclinical models[62], but in humans, the use of pre- or probiotic is not associated with a reduction in the concentration of indoxyl sulfate[63]. The fecal transplantation could be a way to completely modify the microbiota in CKD[64], but we have to keep in mind that we were not able to identify a real specific CKD microbiota[65]. It was also proposed to use AST-120 to reduce the blood concentration of TDUT. Despite efficiency in small clinical trials[66], a large randomized controlled trial was associated with a failure for the primary outcome [67], limiting the interest for the approach. Despite the lack of success in CKD, the benefit of AB-2004, a very close absorbent of AST-120 in autism renew the interest for this approach in the treatment of depression[68]. We think that we have enough preliminary data to suggest that a low protein diet with enrichment in fibers must be tested in a clinical trial. The reduction of TDUT by this approach could be of high interest for patients and easiest to implement than modulation of gut microbiota or use of charcoal.

11. Treatment of depression in CKD patients: results from clinical studies

About 50 % of adult patients with CKD in the were prescribed an antidepressant in a cross-sectional study in more than 9 million of patients with CKD and depression in the United States. Serotonin reuptake inhibitors are the mostly used antidepressants in CKD patients [69]. Antidepressant prescribing was 1.5 fold higher in patients with CKD compared to the general population (16.3 % vs. 11.9 %), matched for age, sex and time of year [70]. In a Dutch nationwide cohort: the prevalence of antidepressant prescription was 5.6 % in CKD stages 4–5, 5.3 % in dialysis patients, and 4.2 % in patients with kidney transplantation (KT), significantly higher than in matched controls. Tricyclic antidepressants were more frequently prescribed in CKD patients [71]

Among 4839 patients with mild to moderate CKD from the CRIC cohort, depressive symptoms were associated with mortality, hospitalization and cardiovascular events non reduced by the antidepressant medication. On the other hand antidepressant use was associated with increased risk of hospitalizations and mortality, even after adjusting on depressive symptoms[72]. In 598 153 US veterans with CKD [73], administration of antidepressants was independently associated with a 1.28- to 1.58- fold increased risk of mortality[73]. No association was found between antidepressant dosage and mortality or hospitalization in elderly patients with moderate CKD [74].

Drug-drug reactions may partially explain the reduced efficiency of antidepressant in often polymedicated CKD patients. Notably, serum concentrations of amitriptyline were decreased by 75 % when the drug was administered concomitantly with polystyrene sulfonate, frequently prescribed in CKD patients [75].

Very few randomized controlled trials evaluating antidepressant exist were conducted in the specific CKD population. The CAST study was the largest randomized controlled trial in patients with CKD stages 3–5 (excluding dialysis patients) evaluating sertraline, gradually increased up to 200 mg/d for 12 weeks, versus placebo. Mean Quick Inventory of Depressive Symptomatology-Clinician Rated (QIDS-C_{16}) score was 14 (a score over 5 indicating depression) in both CKD and control groups, indicating a moderate depression in both groups. Sertraline did not improve depressive symptoms compared with placebo [8]. However, only 19.6 % of patients in the sertraline group received full-dose sertraline, mainly due to digestive adverse events, which may limit the therapeutic response, even though the median taken dose was acceptable (150 mg/d) compared to other studies. Interestingly, post-hoc analyses of the CAST study revealed that elevated plasma hsCRP correlated with somatic symptoms of depression and fatigue, and independently predicted favorable response to sertraline, but not to placebo, in CKD patients. hsCRP levels did not differ over time in the sertraline group while hsCRP increased over time in patients receiving placebo [76,77], supporting the role on inflammation in the severity of depression during CKD.

In hemodialysis patients, the randomized controlled trial by Friedli *et al.* found no benefit of sertraline versus placebo in 30 patients on hemodialysis[78]. The ASCEND randomized controlled trial, comparing cognitive behavioural therapy (CBT) versus sertraline in 120 hemodialysis patients, and found a significant but modest improvement of depressive symptoms at 12 weeks: effect estimate on QIDS-C of −1.84 $_{95\ \%}$CI [-3.54 to −0.13]. Non serious adverse events were more frequent in the sertraline group [79]. However, mean QIDS-C was 11 at baseline, indicating a mild depression. It is worth noting that, in the general population, antidepressants fail to be superior to placebo in mild to moderate depression.

Targeting inflammation seems promising to treat resistant depression. A meta-analysis of randomized clinical trials found that anti-inflammatory drugs, particularly celecoxib, can decrease depressive symptoms[80]. However, the association between antidepressants and anti-inflammatory drugs to potentially increase their efficiency have not been evaluated yet in CKD patients, and the potential use of non-steroidal anti-inflammatory drugs is very limited in this population, given their high risk of adverse events, notably the worsening of kidney function.

Moreover, CKD patients should benefit from non-pharmacological intervention like physical exercise (which was proven effective to alleviate depressive symptoms[81]), CBT, mindful-based stress reduction, peer support programs, who must be developed and adapted to CKD patients. In a Belgian study, structured interventions of psychologists in ESKD patients in hemodialysis resulted in a significant reduction of anxiety and depression and an increased in quality-of-life scores[82].

Patients with CKD undergoing dialysis present a unique opportunity for the development of innovative approaches to treat depression. Future research and clinical trials could explore the potential efficacy of integrating novel interventions, such as repetitive transcranial magnetic stimulation (rTMS), digital therapies, and dietary modifications, tailored specifically to this population. innovative strategies to address depression in patients with chronic kidney disease (CKD) undergoing dialysis could include repetitive transcranial magnetic stimulation (rTMS), digital therapies, and dietary modifications. rTMS, a non-invasive neuromodulation technique, could be implemented during dialysis sessions to target depression without systemic side effects. It has shown efficacy in treatment-resistant depression in other populations and could provide a time-efficient solution for CKD patients [83].

Digital therapies, such as guided internet-based cognitive behavioral therapy (iCBT), may also be valuable during dialysis. Portable devices can deliver these interventions, which have proven effective in the general population [84], but require validation in CKD settings.

Finally, dietary interventions, such as a Mediterranean diet, could address chronic inflammation, a shared factor in CKD progression and depression [85]. These approaches might improve both mental and physical health outcomes.

Future research should focus on these interventions to determine their potential to enhance the quality of life for CKD patients. Effective and potential treatments of depression during CKD are summarized in Table 2.

Table 1
Effects of Uremic toxins on depression during CKD.

Uremic Toxin	Effects on Depression	Biological mechanisms	References
Indoxyl Sulfate	↗	- ↘ brain serotonin - AhR activation - ↗ BBB Permeability - ↗ Neuroinflammation - ↘ brain dopamine	[42–44, 47]
Kynurenic Acid	↗	AhR activation	[39,40]
Paracresyl sulfate	↗	↗ Neuroinflammation	[53]
4-ethylphenyl sulfate (4EPS)	↗	Oligodendrocytes alteration	[54]
Indole−3-Propionic Acid	↘	- Restores GABAergic deficits - ↗ Phosphorylation of ERK1	[56]
Ammonia	↘	- Protection against other uremic toxins? - Restores GABAergic deficits	[57]

AhR: Aryl Hydrocarbon receptor, BBB: blood- brain barrier, GABA: gamma-aminobutyric acid

12. CKD and antidepressant resistance: pharmacological and biological considerations

The evidence is weak in favor of antidepressant efficacy to this date in patients with CKD. Beyond the limitation of available RCT, daily practice demonstrates also a clear trend of treatment resistance. Otherwise, CKD is also an interesting model to understand plausible factors associated with antidepressant resistance. Potential CKD-specific mechanisms involved in resistance to treatment in depression are summarized in Fig. 2.

First, as previously detailed, chronic diseases are associated with lower adherence to treatment which impairs directly efficacy. Pharmacokinetic and drug metabolism alterations due to renal dysfunction could also be involved in treatment resistance and/or higher level of side-effects which in turn alter medication adherence and increase the risk of treatment discontinuation. From a pharmacodynamic point of view, several biological mechanisms associated with antidepressant resistance are common with biological alteration reported during CKD. For instance, chronic inflammation, even in a lower extent, has been described in both contexts, in particular higher plasma level of IL-6, TNF or CRP. Moreover, the kynurenine pathway has been also associated

Table 2
Effective treatments and potential innovative perspectives in the treatment of depression during CKD.

Category	Intervention Type	Description	Advantages	Limitations	References
Effective Treatments	Pharmacological Treatments	First-line: Selective serotonin reuptake inhibitors (SSRIs) serotonin-norepinephrine reuptake inhibitors	- Commonly used in CKD patients	- Limited efficacy - Associated with increased risk of mortality and hospitalization. - Drug interactions - Dose adaptation	[73,76,78, 79,96]
	Psychological Treatments	First-line: Cognitive Behavioral Therapy (CBT), Interpersonal Therapy, Behavioral Activation; Mindfulness-Based Cognitive Therapy, Long-term Psychodynamic Psychotherapy	- Fewer adverse effects compared to pharmacological treatments.	- Modest improvements in depressive symptoms in CKD patients	[82,97]
	Lifestyle Modifications	General lifestyle modifications: - sleep hygiene, - supervised, exercise, - healthy diet, - light therapy for seasonal settings	- Exercise is associated with decreased depressive symptoms in CKD	- Lack of specific evidence for CKD populations	[81,98,99]
Innovative Perspectives	Anti-inflammatory drugs	- Celecoxib	- Could target chronic inflammation associated with both CKD and resistant depression.	- No evidence in CKD - Increased risk of worsening CKD with NSAIDs and other adverse events (gastro-intestinal)	[80]
	AhR inhibitors		- Target tryptophan-derved uremic toxins - Act as antidepressant in mice	Not available in clinical practice	[51]
	Neuromodulation	- First-line: Electroconvulsive Therapy for severe depression, repetitive Transcranial Magnetic Stimulation (rTMS) for treatment-resistant depression - Second-line: adjunctive Transcranial Direct Current Stimulation;	- rTMS could be implemented during dialysis sessions - Non-invasive treatment without systemic side effects. - Has shown promise in treatment-resistant depression.	- Poorly evaluated in CKD	[83]
	Digital Therapies	- First-line: Guided internet-based CBT and internet-based Behavioral Activation for mild-moderate depression - Second-line: adjunctive self-directed digital interventions with clinician support - Third-line: self-directed digital interventions for mild depression	Could be delivered during dialysis using portable devices. Have proven effective in other populations	- Need validation in CKD settings	[84,100]
	Dietary Modifications	- Mediterranean diet - Low protein diet - High fiber diet	- Could target chronic inflammation associated with both CKD progression and depression. - Decrease serum uremic toxin levels	- May be difficult to manage in CKD patients	[60,61,85]
	Complementary and alternative medicine	Adjunctive L-methylfolate, S-adenosyl-L-methionine; Third-line: Omega−3 fatty acids, Lavender, Saffron	- Could improve depressive symptoms in adjunction to antidepressants	- No evidence in CKD	[101]

AhR: Aryl Hydrocarbon receptor, CKD: Chronic Kidney Disease, NSAIDs: Non-steroidal anti-inflammatory drugs, rTMS: repetitive transcranial magnetic stimulation
Figure Legends

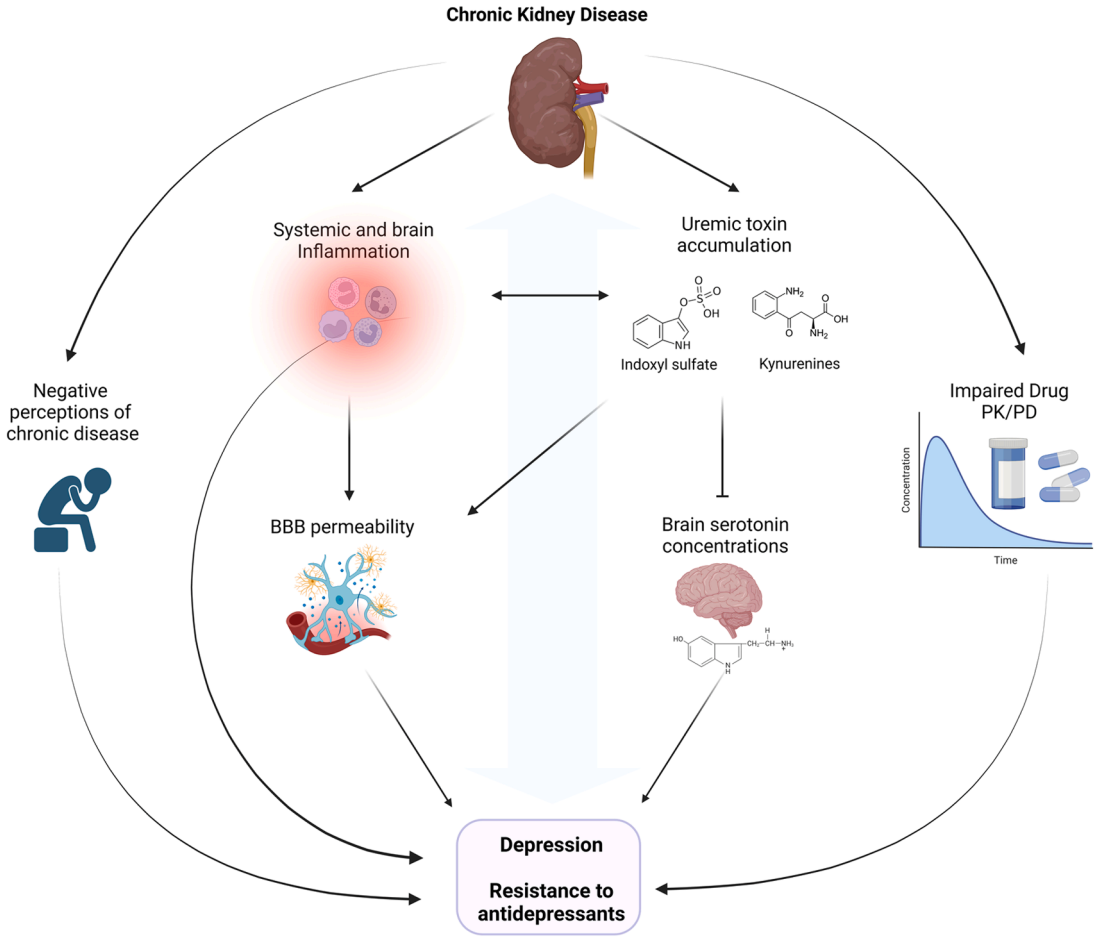

Fig. 2. Potential mechanisms of resistance to treatment in depression during chronic kidney disease. BBB: blood-brain barrier. PK/PD: pharmacokinetics and pharmacodynamics.
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with treatment resistance [86], this latter pathway being probably the consequence of chronic inflammation. Chronic inflammation may also have consequences on central nervous system, notably regarding white matter integrity, via glial cells abnormal activities[31]. Interestingly, measure form brain imaging studies describe white matter integrity modifications also associated in antidepressant response[32] as well as in CKD[87]. Increased blood-brain barrier permeability has been described in models of CKD in rodents, in relation to AhR activation by indoxyl sulfate[44], and in patients with ESKD[12], but also seem an important mechanism of resistance to treatment in depression[88].

13. Depression and kidney transplantation

Prevalence of depression is lower in KT recipients than in CKD patients. In cross-sectional studies depression had still an notable prevalence of 12.5–25 %[89–91]. Depressive symptoms are more frequent in frail KT recipients (26 vs 2.5 %, $p < 0.001$) [92]. Depression is associated with impaired graft function [91] and with decreased immunosuppressant treatment adherence [93]. Post-traumatic stress disorder (PTSD) occur in 21 % of adult KT recipients and 42 % of pediatric patients, and is frequently associated with depression or other psychiatric comorbidities[94]. KT recipients with active coping style less experiment depression and PTSD [91]. Also, in a prospective study, 86 % of candidates to KT display depressive symptoms, which increase with the time on the waitlist. Patients who report depressive symptoms, even minimal, have lower chances to be listed: aHR 0.75, $_{95\,\%}$CI [0.66–0.85] [95].

14. Recommendations for clinical practice

Mental health management should be a cornerstone of the care of CKD patients. In our opinion, all CKD patients must be screened for depression, while remaining cautious of aspecific symptoms such as fatigue, and this screening must be repeated over time. CKD patients must have access to interdisciplinary care, notably to psychologists trained in chronic diseases, and psychological follow-up must be widely proposed. In France, the legislation has introduced since 2019 a "CKD Package" to facilitate access for Stage 4 and 5 CKD patients to paramedical consultations, including with psychologists. Once diagnosed with depression, these patients should be referred to trained psychiatrists. Physicians must be careful to adapt the prescribed dose of antidepressants to the kidney function of CKD patients, to increase the doses gradually if necessary, and to consider drug interactions in these often polymedicated patients. All psychiatrists should be aware of the particularities of depression during CKD, notably the risk of antidepressant resistance.

15. Conclusions

Relationships between CKD and depression remain complex and not yet fully understood. Both conditions influence each other negatively, with one exacerbating the prognosis of the other. Despite the frequent use of antidepressants in this population, their efficacy remains limited, likely due to the specific pathophysiological changes associated with CKD. Raising evidence suggests that chronic inflammation, in relation to

uremic toxin accumulation like kynurenines and indoxyl sulfate during CKD, appears as an important mechanism for treatment resistance in depression. Given this challenge, future research should consider uremic toxins and inflammation as potential therapeutic targets, in order to improve the prognosis of depression in CKD patients

CRediT authorship contribution statement

AL, SB, SB, RB and MB performed the literature research and wrote parts of the manuscript.

AL and MB coordinated the review and wrote the initial draft of the manuscript.

All authors revised it critically and approved the final version of the manuscript.

CRediT authorship contribution statement

Bobot Mickaël: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Investigation, Conceptualization. **Belzeaux Raoul:** Writing – review & editing, Investigation, Data curation, Conceptualization. **Lefrère Antoine:** Writing – review & editing, Writing – original draft, Visualization, Investigation, Conceptualization. **Bobot Stanislas:** Writing – review & editing, Writing – original draft, Investigation. **Burtey Stéphane:** Writing – review & editing, Investigation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

Data availability

No data was used for the research described in the article.

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