

1 Repurposing Amantadine and Memantine for COVID-19: Guanylate Kinases Might Pave  
2 the Road towards Novel SARS CoV-2 and Anti Neoplastic Therapeutics.

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20 *To the Editor,*

21 Guanylate kinase 1 (GK) is a highly specific cytosolic nucleoside monophosphate kinase  
22 that is considered an essential enzyme in nucleotide metabolism pathways that solely  
23 catalyzes the phosphorylation of guanosine monophosphate to diphosphate which acts as a  
24 substrate for GTP/dGTP synthesis used for nucleic acid or cyclic GMP synthesis.  
25 Importantly, GK plays a critical and essential role in metabolic activation of antiviral and  
26 antineoplastic nucleoside-analogs prodrugs, including 6-thioguanine, 6-mercaptopurine,  
27 acyclovir, ganciclovir and cyclopropavir. Interestingly, GK has been suggested to play a  
28 fundamental role in SARS CoV-2 replication and in-vitro experiments testing the potential  
29 benefits of GK inhibitors were suggested by Renz et al. (1) and other colleagues have  
30 confirmed a GK role in SARS CoV-2 replication while adding more targets to be  
31 considered(2).

32 However, we would like to emphasize that specific GK inhibitors, e.g. the nucleotide  
33 analogue Ap5G, were only used to experimentally and owing to the various physiological  
34 known and potentially yet to be discovered physiological functions of GK we suggest that  
35 its specific inhibitors should be carefully assessed as regards to their safety to manage  
36 COVID-19. On the other hand, GK gene was localized in 1980 on chromosome one and  
37 later its encoding was described and it is currently readily available  
38 [<https://www.ncbi.nlm.nih.gov/gene?Db=gene&Cmd=DetailsSearch&Term=2987>] and  
39 interestingly, genetic variants of other kinases have been described to negatively impact  
40 their action (3), thus if GK was proved crucial for SARS CoV-2 replication, its genetic  
41 polymorphisms might help to further explain some encountered idiosyncratic COVID-19  
42 morbidity and mortality outcomes(4). Moreover, overexpression of GK gene was

43 previously suggested to be involved in the pathogenesis of some tumors together with an  
44 unfulfilled call for exploration of some unexplored physiological functions that GK might  
45 be involved (5) and we wish to repeat this call for the best interests of scientific medical  
46 and pharmacological research. Additionally, we recommend testing another potential that  
47 the non-authentic membrane-associated guanylate kinases, that contain GK like domains,  
48 might share in SARS CoV-2 pathogenesis as these enzymes are known to regulate the  
49 CNS NMDA receptors and their potential SARS CoV-2 interaction should be investigated  
50 especially if the preliminary reports showing a potential benefit of the NMDA receptor  
51 antagonist amantadine, which is currently used in treatment of parkinsonism and was used  
52 in treatment and prophylaxis of influenza A virus infection before no longer recommended  
53 because of viral resistance, proved clinically significant (6, 7) as we postulate that SARS  
54 CoV-2 is still naïve and that amantadine uncompetitive NMDA antagonism might involve  
55 inhibition of those membrane associated guanylate kinases and/or GK, to be also noted that  
56 invitro antineoplastic properties of amantadine have been previously described.

57 Similarly, memantine, a dimethyl derivative of amantadine, an EMEA and FDA approved  
58 drug for treatment of moderate to severe Alzheimer's disease, has been suggested to possess  
59 beneficial effects in management of COVID-19 via several mechanisms (8). Memantine  
60 is known to possess a higher affinity and more potent antagonism towards NMDA  
61 receptors than amantadine, thus the same, and potentially better, suggested interaction with  
62 GKs might be also applicable for memantine. Notably, both drugs have been suggested for  
63 COVID-19 management basing on their anti-inflammatory and immune-modulatory  
64 properties(9) as well as potential beneficial lysosomal dependent and neuroprotective  
65 effects(10). Finally, we recommend that a short course of amantadine might be first

considered to be tested for selected pediatric severe to critical COVID-19 patients and of memantine for the adult and geriatric severe to critical cases while considering the potential contraindications, dosage modifications and drug-drug interactions.

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None

#### **Conflict of interest**

The author declares that there is no conflict of interest

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