Novel agents for the treatment of delirium: A proposal for a multimodal approach

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Introduction

Delirium is a DSM-5 recognized syndrome characterized by impairment in attention and consciousness occurring in susceptible elderly and critically ill patients.

Precise etiologic mechanisms of delirium are yet to be elucidated; our current understanding describes delirium as a state of multifactorial global brain disfunction resulting from a complex interaction between neuronal aging, neuroinflammation, oxidative stress, neuro-endocrine dysregulation, and circadian dysregulation with their additive effects on neurotransmitter synthesis/availability.

Occurrence rates are estimated to be between 14-56% in elderly hospitalized patients. **Mortality rates associated with delirium are estimated between 25-33%.** Estimated economic burden of delirium ranges between **$38 to $152 billion annually.**

Despite the tremendous burden of disease, there is no FDA-approved treatment for delirium and therefore clinicians are forced to look elsewhere and to 'borrow' and repurpose available medications approved for other indications. Reliance on psychotropic medications in treating delirium and associated behavioral disturbances results in psychiatrists being identified as experts in this field tasked with identifying effective, yet safe approaches in delirium treatment.

Here we propose examining two novel approaches to treatment of delirium:

1. An **anti-inflammatory approach**, as inflammatory markers such as IL-6 and TNF have been shown to be elevated in delirious patients.
2. A **pro-cholinergic approach,** as acetylcholine dysregulation is also believed to play a role in the etiology of delirium.

Anti-Inflammatory Approach

Recent years have seen an explosion in the number and variety of novel inflammatory agents, especially monoclonal antibody therapeutics which work by directly inhibiting inflammatory cytokines such as TNF, IL-1 and IL-6. The COVID-19 pandemic and lack of efficacious treatments for severe cases of COVID-19 lead to increased use of novel anti-inflammatory agents in an attempt to treat severely ill patients infected with COVID-19, many of whom likely suffered simultaneously from delirium. Several classes of agents suspected of having effect on delirium were found to be of interest, including a group of IL-6 inhibitors.

Tocilizumab (IL-6 inhibitor) has been studied for its effects on mental status. It, however failed to address depressive symptoms or improve quality of life. A possible explanation may be its failure to simultaneously block IL-1 and TNF or its limited ability to cross the blood-brain barrier.
Sarilumab (another IL-6 inhibitor) crosses the blood-brain barrier more readily and has been experimentally used in treatment of COVID-19. There are, however, no reported cases of its utility in delirium treatment so far.

Novel Pharmaceutical Proposal:
Given the role of the neuroinflammatory cascade in delirium, we propose investigating the class of **GM-CSF inhibitors**, such as **Otilimab or TMJ2,** with more robust and comprehensive anti-inflammatory properties as a class of medications to be considered in treating delirium.

Unlike the individual cytokine (TNF, IL-6) inhibitors described above, **GM-CSF inhibitors** disrupt inflammatory response at different pathways and may be potentially more useful in managing the complex delirium cascade. They may reverse delirium by:

- Inhibiting the cytokine response (IL-1, IL-6, TNF)
- Limiting the chemotaxis (IL-8)
- Reducing cell degradation (via H_2O_2, MMPs), and
- Blunting the T- and B-cell response

GM-CSF inhibitors have already been shown to be effective in and approved for the treatment of inflammatory conditions and have been effective in treatment of inflammatory processes of COVID-19. Otilimab was investigated in a large double blinded placebo-controlled study of patients critically ill with COVID-19.
Treatment benefits (that did not account for delirium) did not reach statistical significance in the general population, but otilimab was shown to have benefits in patients over the age of 70, a group that likely suffers a high burden of delirium. At this point, considering that otilimab is both available and also used for critically ill patients (including COVID-19 patients), it would make sense to examine its potential in addressing delirium.

Multisystem Integration Failure Hypothesis of Delirium

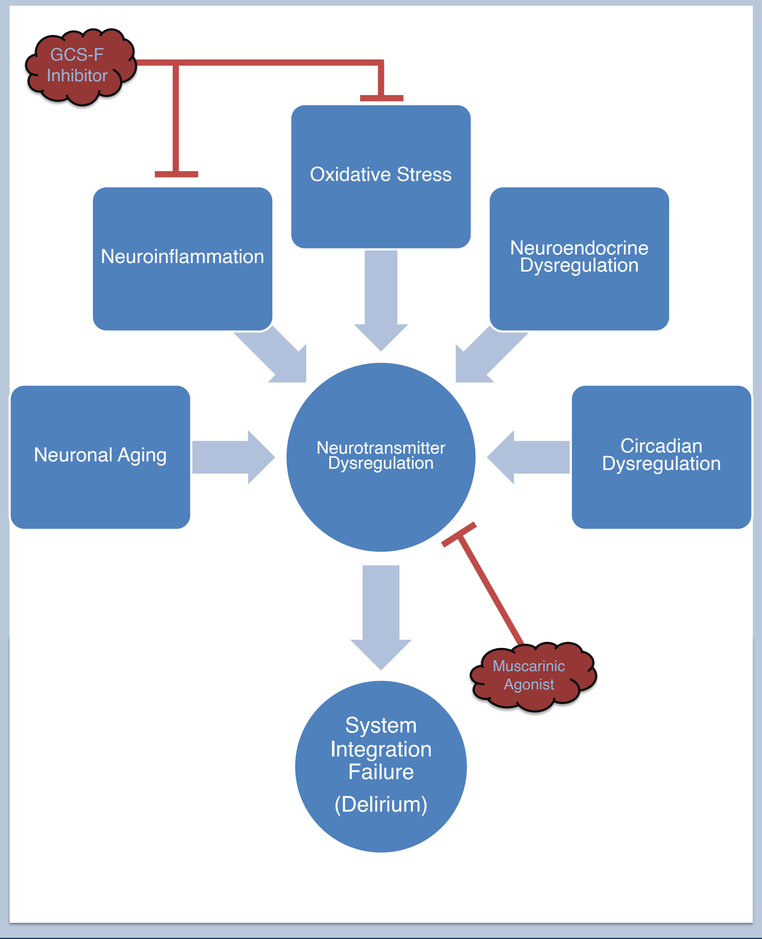

Figure 1. A flowsheet representation of the complex pathophysiology outlined in System's Integration Failure Hypothesis (Maldonado 2017). Muscarinic Agonists could help to alter the state of neurotransmitter dysregulation, notably the decreased amount of Ach produced and utilized in delirious brains. GCS-F Inhibitors could help decrease the overall inflammatory stress present in the delirious brain.

Pro-Cholingeric Approach

Acetylcholine dysregulation ('anticholinergic surge') has long been implicated in delirium.

Delirious brains have been observed to be in a state of acetylcholine deficit.

- The multi-system integration failure hypothesis of delirium describes the neurotransmitter dysregulation that takes place in delirium

The propensity of anti-cholinergic medications to incite delirium implicates the cholinergic system's role in cognitive homeostasis.

- Prior studies suggest some efficacy of acetylcholinesterase inhibitors in the treatment of delirium. The utility of acetylcholinesterase inhibitors may sometimes be overshadowed by side-effects that include nausea, diarrhea, vomiting, decreased appetite, dyspepsia, anorexia, muscle cramps, fatigue, insomnia, dizziness, and headache.

Novel Pharmaceutical Proposal:
Given the role of acetylcholine and the anticholinergic surge associated with delirious states, we propose investigating a different pro-cholinergic compound in the treatment of delirium.

- **Xanomeline** is a pro-cholinergic M-receptor agonist. It is currently studied in combination with **Trospium**, a peripheral anticholinergic. These medications are now administered together to create a net-positive pro-cholinergic state in the brain while at the same time limiting intolerable peripheral cholinergic symptoms such as increased secretions, and GI effects, which were common to prior generations of pro-cholinergic medications.
- This combination of medications, called **KarXT**, may be useful in reversing the anti-cholinergic state of the delirious brain (in addition to treating schizophrenia and cognitive impairment, the targets of current clinical trials).
- **KarXT**, currently in Phase III clinical trials as an antipsychotic, should also be considered a viable candidate for delirium treatment once FDA-approved.

Conclusion

Our current pharmacological approaches to delirium are limited.

- We have been limited to the same medications for decades.
- These medications can target only the behavioral dysregulation or sleep-wake cycle disturbances.

We propose a multifactorial and novel approach to delirium treatment

- **KarXT** targets cholinergic circuitry and aims to restore AcH balance via direct M-receptor agonism.
- **Otilimab and TMJ2** address the entire inflammatory cascade via GM-CSF inhibition.
- These medications can be used individually or, possibly, together, synergistically targeting acetylcholine dysregulation as well as the inflammatory cascade implicated in the pathogenesis of delirium.

At this stage, it would be unrealistic to expect that either of these medications could be initiated solely to treat delirium. We should, however, at least be mindful of their use in severely ill patients with delirium to be able to observe if they are effective in resolving delirium. Such observations would then form a foundation on which we can build and obtain further evidence in this direction.

Citations

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