PREVENTION AND TREATMENT OF POSTOPERATIVE DELIRIUM IN THE ELDERLY, NON-CRITICALLY ILL PEOPLE: A LITERATURE REVIEW

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Abstract
Delirium is a common yet severely underdiagnosed neuropsychiatric condition with short and long spanning implications regarding the risk of death, quality of life and economic burden. There is a moderate body of evidence when it comes to delirium in an ICU or medical setting, whereas data on this pathology in a surgical setting is sparse. In this article, we aim to converge all the relevant and up-to-date evidence on preventing and treating postoperative delirium. We have searched the PubMed and Cochrane databases with the following keywords: “delirium”, “postoperative”, “prevention”, “treatment”, “surgery”, “elderly”. There are currently no validated markers to determine the persons at risk of developing postoperative delirium. No current guidelines exist on preventing or treating postoperative delirium. Even so, multicompartment nonpharmacological interventions like early mobilisation, hearing and visual orientation, healthy sleeping routines etc. seem to have positive results in preventing delirium, but have no effect in treating it once it develops. Hitherto, there is currently no consensus when it comes to pharmacological prevention or treatment with the literature being divided due to a low number of randomised controlled studies with different terminology, high heterogeneity and poorly reported adverse effects. Amid this debate, there are still promising molecules like suvorexant or dexmedetomidine with positive outcomes in preventing postoperative delirium but they are still far away from clinical validation. In conclusion, this important and oftenly missed topic needs further study in a more homogenous and controlled manner at all levels – basic science, translational science and clinical trials.

Key Words: “delirium”, “postoperative”, “prevention”, “treatment”, “elderly”, “surgery”

INTRODUCTION
Delirium is a common neuropsychiatric affliction, frequently underdiagnosed and undertreated, with severe long and short-term outcomes, increased perioperative risk of death and a marked economic burden ranging up to and exceeding 152 billion $ per year in the USA, rivaling the health care costs of Diabetes Mellitus (1-5). Delirium is represented by the sudden onset of cognitive impairment and altered consciousness. The syndrome incorporates fluctuations of consciousness over the course of a day, decreased focus and evidence that the cause is organic, in direct relationship with the underlying

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condition. Although delirium has been studied with mixed results in a plethora of settings (medical, surgical and ICU), the prevention or treatment of the elderly non-critically ill surgical patient is one of the least studied subjects delirium-wise. The aim of our review is to converge all the relevant data on this topic in this article. As such, in a surgical setting, the incidence varies from 11 to 51%, with Orthopedic Surgery and Cardiac Surgery leading in the top, the target population being the elderly, most medically complex patients (2). In general, the incidence is higher in the acute procedures compared to the elective ones, such as orthopedic repair fractures (21.7%) vs elective orthopedic surgeries (12.1%) and is also dependent on the complexity of the surgical act – valve replacements having higher rates of delirium than the less difficult bypass surgery (6, 7). That is not to say that minor surgeries are without delirium risks. A study aiming to explore the incidence of delirium following cataract surgery found that 4.4% of their subjects manifested immediate postoperative delirium and that older age and more frequent use of benzodiazepine medications were risk factors [8]. Another study found that the incidence of postoperative delirium in a lot of 358 people undergoing elective Trans Urethral Resection of the Prostate (TURP) was 7.8%, with old age and pain intensity after surgery being found as risk factors (9). The implications of these high rates are far reaching and span over both the medical and economical aspects of patient care. It has been shown that persons who develop delirium are at a greater risk of death (both in the hospital and after discharge), long-term cognitive decline, lengthy hospitalizations, reduced physical function for more than 30 days after the procedure, reduced quality of life and need of institutionalization (2)(4)(10). Thus, the interest in this area is spurred, as studies have shown delirium can be prevented in as much as 30-40% of the cases, it’s severity reduced, as well as the total number of days with delirium minimized (11, 12, 13). Multiple theories have been proposed on the pathogenesis of delirium and the seven most popular ones are: the neuro-inflammation, the neuronal aging, the oxidative stress, the neurotransmitter, the neuroendocrine, the diurnal dysregulation or melatonin dysregulation and the network disconnectivity hypotheses (14). The neuro-inflammatory theory postulates that the acute peripheral inflammation induces the activation of the parenchymal cells and the expression of pro-inflammatory cytokines at the CNS level which in turn create an imbalance in the neural and synaptic environment, all of this leading to the neurobehavioural symptoms of delirium. The neuronal aging theory stands on the concept of homeostenosis which states that even though an elder can be functional and healthy into old age, he is more prone to illness due to a lack of neuronal physiological reserve. The oxidative stress theory stands on the concept that hypoperfusion induces oxidative damage in cells with the generation of reactive oxygen and nitrogen species. The neurotransmitter hypothesis states that delirium is linked to a low central cholinergic transmission mixed with an increased dopaminergic activity, both of which have an effect on the GABA-ergic and glutamatergic pathways. The neuroendocrine theory suggests that neurons enter a vulnerable state due to abnormally high glucocorticoids levels which makes them unable to survive after acute metabolic insults. The diurnal dysregulation and melatonin dysregulation hypothesis both rest on the the fact that the impairment of the normal 24-hours sleep cycle and of the physiological sleep stages lead to delirium through an imbalance in natural-killer cells, reduced IL-2 production and other inflammatory mediated mechanisms. Finally, the network disconnectivity theory states that different delirium subtypes correspond to different neurotransmitter-specific alterations with the main culprits being the cholinergic and GABA-ergic systems. It is unlikely that delirium is the sole result of just one of these theories and more probable that the above mechanisms interact with one another. As such, delirium occurs as the interplay of a patient’s predisposing factors and the surgical and anesthesiological stress sustained in the perioperative period. The single most common risk factor is advanced age (>65 years old). Other than this, predisposing factors include: preexisting neuropsychiatric conditions, habitual use of psychotropic medications, poor physical status, diabetes mellitus, atrial fibrillation, atherosclerosis and tobacco use. Precipitating factors include surgery duration and complexity, blood lose or transfusion, depth of anesthesia, postoperative complications such as infections, pain, sleep disruption or use of physical restraints (15). Different surgical fields have different weighing risk factors for delirium. For example, in vascular surgery, elderly patients having renal failure, previous strokes or male sex are strongly associated with postoperative delirium whereas in deep brain stimulation surgery for Parkinson disease, white matter atrophy in the temporal stem is a factor predictive of postoperative delirium (16) (17). Also, in elderly patients (>65 years old) undergoing non-cardiac surgery and especially in colorectal cancer operations, hypoalbuminemia was found to be a strong risk factor associated with postoperative delirium (18) (19). The problem is that risk factors alone cannot predict the onset of delirium. To remedy this, new promising studies are using the pathophysiological theories of this illness to find humoral or imagistic vulnerability markers that can estimate the probability of postoperative delirium or its severity. Such a study (20) revealed that the neuroticism score, the amplitude of low-frequency fluctuations in the dorsolateral prefrontal cortex and the gray matter density in the caudate/suprachiasmatic nucleus are predisposing factors. A postoperative delirium prediction model including this variables showed a correct classification rate of 86%. Other studies seem to indicate that the neopterin levels in the cerebrospinal fluid can be used as a predictor of both the onset of postoperative delirium and its poor outcomes (21) (22). The CRP could also be used as a biomarker for predicting delirium in non-cardiac surgery, but its low specificity for this pathology could be a hindrance (23). Also, the cerebrospinal fluid beta-amyloid 1-42 was proposed as a possible prediction marker, but studies seem to talk at cross purposes on the matter of its usefulness (24) (25). It is worth mentioning, though, that there are far too few studies on the CSF B-amyloid 1-42 as a marker for delirium and the subject warrants further research to come to a definitive answer. On another note, reduced MMSE scores on the delayed recall and working memory domains appear to be predictors of delirium (26). It is important to bear in mind that the studies regarding the prediction of the onset of postoperative delirium are too few and far between and is a Romanian Journal of Psychiatry, vol. XX, No.3, 2018
field worth investigating deeper. Clinically, delirium presents itself in 3 forms: hyperactive, hypoactive and mixed. The hyperactive form is the most recognisable one by the medical staff as it's presented with hypervigilance and psychomotor agitation. Conversely, hypoactive delirium mainly goes unnoticed because the lethargy and slowing might not be readily evident, but also carries a worse prognosis than the hyperactive one and it occurs more often. The mixed form is a combination between the aforementioned two.

DIAGNOSIS
Postoperative delirium is mainly a clinical diagnosis and is prone to the subjectivity of the observer. Studies have shown that even with a standardized assessment tool, its sensitivity and specificity can decrease if used by an untrained professional (2). Henceforth, numerous clinical tools have been developed to satisfy this need. By far, the most used and studied tool is the Confusion Assessment Method (CAM) and its variants like CAM-ICU. The CAM tool assesses the presence, severity, and fluctuation of 9 delirium features: acute onset, inattention, disorganized thinking, altered level of consciousness, disorientation, memory impairment, perceptual disturbances, psychomotor agitation or retardation, and altered sleep-wake cycle. The presence of delirium requires the presence of acute onset and inattention plus one of either disorganized thinking or altered level of consciousness. A 2010 systematic review validated CAM as having the best available evidence for its use as a bedside delirium tool (27). More than this, CAM only takes around 5 minutes to administer. Interestingly enough, this same study found that the MMSE scale was the least useful at identifying patients with delirium. There is a plethora of other tools for identifying delirium adapted for various situations such as the Short Orientation Memory Concentration Test (28) which is best suited in short outpatient encounters, or the Nursing Delirium Screening Scale (29) which is best used in an inpatient setting with continuous surveillance. Newer clinical tools that need further testing include the Delirium Observational Screening Scale (30), the 4AT (31) and the Months Of The Year Backwards (32). Still, postoperative delirium remains under-recognized in the surgical setting at all levels - doctors, nurses, family - and its symptoms are poorly documented in the medical notes, especially when superimposed on pre-existing dementia (33). This could be due to lack of information on the subject, poor assessment tools and poor nomenclature. Thus, further insight and clarifications on the matter is much needed.

NON-PHARMACOLOGICAL PREVENTION AND TREATMENT
For the sake of clarity, we have included in the non-pharmacological category all the interventions not related to psychoactive medication. As such, blood transfusions and saline infusions and physical preconditioning will all be described here.

Many of the risk factors for delirium are amenable by simple non-pharmacological measures. While some risk factors are immutable (age, preexisting cognitive impairment, multiple comorbidities), others are not (sleep imbalance, immobility, visual and hearing impairment, dehydration, social isolation, physical restraint use, psychoactive polypharmacology, pain, hypoxia, Foley catheterization and more) (10). However, things are more complicated than they look at a first glance. Even though a lot of the risk factors are common between medical and surgical delirium patients, there are still some that are particular to the latter (higher pain, immobility, etc.). Thus, prevention and treatment of delirium in a surgical setting might require a different approach and could be met with a different set of challenges than in a medical setting.

Some of these risk factors can be easily targeted non-pharmacological in a multidisciplinary manner or with proactive geriatric consultations. The hallmark study that addressed in a nonpharmacological manner 6 of the above risk factors – cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment, dehydration – was developed by Inouye et all (12) and was met with resounding success in both decreasing the incidence and the number of delirium episodes. Later, this whole strategy has become known as the Hospital Elder Life Program (HELP) and has been successfully implemented in multiple countries across the world. The initial study was focused on medical wards patients with delirium and thus some of the components of HELP could not be accurately reproduced in a surgical setting. To address this, numerous adaptations of HELP have been developed, all sharing the basic strategies summarized in Table 1 (34) and showing similar efficacy in preventing delirium in oral cancer surgery (35), hip surgery (36) or abdominal surgery (37).

<table>
<thead>
<tr>
<th>Common strategies for multicomponent postoperative delirium prevention</th>
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<tr>
<td>Orient to setting</td>
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<tr>
<td>Physical therapy, increase mobility</td>
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<tr>
<td>Promote healthy sleep</td>
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<td>Proactive geriatric consultation</td>
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<td>Correct medication management</td>
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<td>- Optimal pain control</td>
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<tr>
<td>- Avoidance of polypharmacy</td>
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<tr>
<td>- Lower usage of psychoactive medication</td>
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<tr>
<td>Ensure readily access to contacts, hearing aids, dentures, glasses</td>
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<td>Education of the healthcare personnel</td>
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Table 1 (Adaptation from Katie J. Schenning et al., Postoperative Delirium in the Geriatric Patient (34))

All in all, a recent Cochrane Review revealed that the incidence of delirium had a risk ratio of 0.69 (95% confidence interval, 0.59-0.81) when comparing multicomponent non-pharmacologic intervention to normal hospital care (38). To corroborate this, a systematic review on the effectiveness of multicomponent interventions on the incidence of delirium in hospitalized older patients with hip fracture found that the incidence of postoperative delirium was lower in the intervention group and also that the cognitive decline was higher in the control group compared to the intervention one (39). On the other hand, the same systematic review did not shed light on the duration or the severity of the delirium. In regards with duration, the studies are not completely relevant, 3 studies could not be pooled, 4 studies reported significantly lower delirium duration in the intervention group and 2 studies did not find it statistically significant.
Interestingly enough and warranting further research, this systematic review found only 3 studies on the functional and mobility status and only one of them found that a significantly higher number of participants were walking independently with walking aids on discharge in the intervention group compared to the control one. Another systematic review found that the HELP program is effective at reducing delirium incidence and rate of fall, with a trend towards reducing length of stay and preventing institutionalization (40). A great deal of studies (41) (42) have come to the conclusion that many of the multicomponent non-pharmacological interventions do not require trained professionals to put them in practice, but rather similar results can be achieved with family members, caregivers or volunteers. One drawback is that these studies were focused on the medical wards patients, whereas there is currently a scant body of evidence on the surgical patients. One of the few randomized studies found evaluated the effects of involving family members in the management strategies for delirium in a post cardiac surgery setting (43). The study showed promising results, with the intervention group presenting better psycho-functional recovery scores when compared to the control. However, its limitations were important — low number of participants (14 in usual care group and 16 in the intervention one) and most of all, the intervention happened after the surgery so there was no pre-operative preventing component in it. We believe this specific topic needs further evidence-based attention in a multitude of surgical specialties and we think that the simple involvement of families or volunteers in preventing delirium (for eg. reorientation, restoration of sensory perception, oral hydration etc.) in a surgical setting could yield similar results to the medical one while also improving the cost-effectives of the whole process.

In addition to the multicomponent strategies presented above, numerous other non-pharmacological methods have been tested in trying to prevent postoperative delirium. Blood transfusions used to correct anemia have mixed evidence when it comes to postoperative delirium prevention (44) (45). Hypertonic saline solution, widely used in the resuscitation of the traumatic hemorrhagic shock, has been proven to have beneficial effects on the immune cell function and the subsequent inflammation. Thus, a novel approach uses hypertonic saline solutions to prevent delirium with promising results (46) (47) (48). On the other hand, preoperative exercise capacity is an independent factor in the development of postoperative delirium in elective cardiac surgery (49). It remains to be seen if physically preconditioning a patient at risk before an elective surgery can reduce the incidence of delirium. Bright light therapy and music therapy, although having strong recommendations against their use in an ICU setting, might prove effective in a surgical setting where the patients have a different biological profile (50).

Further research should investigate the effect of multicomponent nonpharmacological interventions on the biological markers associated with delirium (IL1, IL6, TNFalpha, cortisol, CRP, etc.). Also, it is important to keep in mind that once postoperative delirium develops, the current evidence does not support the efficacy of multicomponent non-pharmacological interventions to treat it (51).

PHARMACOLOGICAL PREVENTION AND TREATMENT

Multiple pharmacological therapies have been researched regarding their efficacy in preventing and / or treating delirium. Summarized below are the main classes most investigated.

A) Typical antipsychotics

Of the typical antipsychotics, probably the most studied is Haloperidol. Although there is much data regarding the prevention and treatment of postoperative delirium in the ICU patients, that is not the case with the ordinary postoperative delirium patient on the surgical wards. Moreover, results regarding the prevention and treatment with haloperidol of the ICU patients (52) (53) cannot be extrapolated to the normal postoperative delirium patients because the former have a poorer biological status and a different pharmacological safety profile. Taking this into consideration, data on the run-of-the-mill postoperative delirium patients is divisive. One study came to the conclusion that prophylaxis with haloperidol can significantly reduce the incidence of delirium in the elderly (54), while Fukata et al. states that, after conducting a randomized, open-label prospective trial on the effects of haloperidol prophylaxis on postoperative delirium in the elderly, there were no significant differences between the intervention and the control groups (55). In all of the above studies, the prophylaxis was made with low dose haloperidol, but the definition of that low dose and the method of administration (eg. 1 time 2.5 mg bolus, 3 times per day x 0.5 mg, continuous iv 0.1 mg/g x 12h) differs vastly which can be a confounding factor in pooling the studies.

On the other hand, regardless of its ability to prevent delirium, it seems haloperidol might be useful in reducing the duration, severity and length of stay according to the above meta-analysis (54), but even this is still a matter of debate. As such, a Cochrane Database Systematic Review updated in 2018 found that typical antipsychotics did not reduce delirium severity, resolve symptoms or alter mortality (56). This dichotomy only reinforces the need for high quality studies and for further research in this matter. Once postoperative delirium develops in non-ICU patients, treating it with haloperidol is met with a paucity of evidence. The same Cochrane Review found that typical antipsychotics did not resolve delirium symptoms compared to nonantipsychotic drug regimens, but also marked it as a very low-quality evidence. This seems to be corroborated by another systematic review, also taking into consideration the same very-low quality evidence (57). On the opposite side stands Kishi et al. whose meta-analysis came to the conclusion that antipsychotics were significantly superior to placebo in response rate in the non-ICU setting (58).

On the positive side, in most of the above studies there were no significant side-effects present in the non-ICU delirious patients (including similar QTc in both the intervention and the control groups) at the administration of the low-dose haloperidol prophylaxis. To top it, Schrijver EJ et al. found that low dose oral haloperidol does not seem to prolong the QTc interval in the elderly acutely hospitalized (59). This warrants further research into this matter, as this new finding in the safety profile of haloperidol in the treatment of non-ICU patients with

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delirium could be a pivotal shift into issuing guidelines. At the moment, taking into consideration the possible side-effects of haloperidol (cardiac arrhythmias, QTc prolongation, pancytopenia, extrapyramidal reactions etc.), the current guidelines state that haloperidol should not be used for either prophylaxis or treatment of postoperative delirium and its use in a delirium context should be reserved only for the patients with severe psychosis and agitation, that present a risk to themselves or others (60).

**B) Atypical antipsychotics**

- **Olanzapine**

Olanzapine is a second generation antipsychotic with antagonistic effects on the serotonin and dopamine postsynaptic receptors. Although there are not nearly as many studies conducted on the topic of postoperative delirium on Olanzapine as there are on Haloperidol, there is still enough data to form a modicum of opinion. As is the case with Haloperidol and, for all intents and purposes with all antipsychotics, there are not so many studies investigating the non-ICU surgical setting as there are on the topic of ICU patients. Taking this into consideration, a study comparing Olanzapine vs Placebo for the prevention of postoperative delirium in elective hip-replacement patients found that the administration of 10 mg of oral Olanzapine perioperatively was significantly associated with a lower incidence of delirium. However, delirium lasted longer and was more severe in the olanzapine group, and patients treated with olanzapine had lower albumin and calcium levels, increased prolactin levels and abnormal lipid and glucose metabolism (61). Another inquiry on the same database of the aforementioned study found that patients who received Olanzapine had an 83% risk of developing delirium if they received more than 42.5 mg equivalents of intra-operative morphine, had ≥74 years old and had a mean arterial pressure < 90 mmHg at the presurgical screening visit (62). With more studies and data like this, lines could be drawn to isolate a target group on which Olanzapine is still enough data to form a modicum of opinion. As is the case with Haloperidol and, for all intents and purposes with all antipsychotics, there are not so many studies investigating the non-ICU surgical setting as there are on the topic of ICU patients. Taking this into consideration, a study comparing Olanzapine vs Placebo for the prevention of postoperative delirium in elective hip-replacement patients found that the administration of 10 mg of oral Olanzapine perioperatively was significantly associated with a lower incidence of delirium. However, delirium lasted longer and was more severe in the olanzapine group, and patients treated with olanzapine had lower albumin and calcium levels, increased prolactin levels and abnormal lipid and glucose metabolism (61). Another inquiry on the same database of the aforementioned study found that patients who received Olanzapine had an 83% risk of developing delirium if they received more than 42.5 mg equivalents of intra-operative morphine, had ≥74 years old and had a mean arterial pressure < 90 mmHg at the presurgical screening visit (62). With more studies and data like this, lines could be drawn to isolate a target group on which Olanzapine attains optimal results as a prophylactic agent.

When it comes to treating postoperative delirium, in their meta-analysis, Kishi et al. found that Olanzapine did not outperform Haloperidol when it came to alleviating the delirium, but the former was superior to the latter regarding time to response (TTR) and the incidence of dystonia. Olanzapine was also associated with a higher incidence of dry mouth compared to placebo (58).

- **Quetiapine, Risperidone and Ziprasidone**

Data on these three antipsychotics is scarcer even than data on the former two – Haloperidol and Olanzapine. Quetiapine seems to have a positive outcome on time to response, response rate and delirium severity scale scores at study endpoint when compared both with placebo and haloperidol (58). Also, a study on the prevention and treatment of postoperative delirium in the elderly following elective spinal surgery came to the conclusion that adding quetiapine to haloperidol results in a delirium resolution an average of 3.5 days faster that haloperidol alone (P=0.001) and decreases agitation and length-of-stay in hospital (P=0.02 and P=0.05 respectively) (63). Risperidone, in turn, is sometimes preferred because it is less sedating. One study found that one dose of 1 mg of risperidone decreased the incidence of postoperative delirium after cardiac surgery with cardiopulmonary bypass by 20% (64). Building on this idea, Grover et al. states that risperidone is as efficacious as haloperidol in treating delirium, but as a downside he did not study its effects on preventing delirium (65). Ziprasidone is by far the least studied of the above antipsychotics when it comes to delirium. No studies were found on the prevention and/or treatment of postoperative delirium on non-critically ill patients and one of the few studies on the ICU patients found no significant difference in the outcomes of treating delirium with ziprasidone, haloperidol and placebo (66). It is important to note that most of the research on the topic at hand involving the above 3 atypical antipsychotics is offset by small sample populations and the road to a more definitive answer is long and fraught with scientific uncertainty.

- **Other atypical antipsychotics**

When it comes to the quality of evidence on atypical antipsychotics including Amisulpride and Aripiprazole, it is important to note that Rivière J et al. mentioned in their 2018 systematic review that there are no randomized controlled studies to support their efficacy and tolerability delirium-wise (67). These two atypical antipsychotics are by far the least studied in a surgical setting. Amisulpride has been shown to provide good results in the treatment of post-surgical delirium, but no data is available for its use in prevention and, more so, the results are limited by a small population sample (68). On the other hand, to the best of our knowledge, aripiprazole has not been tested in a controlled manner in a surgical delirium setting. If we were to extrapolate its results in a medical/palliative care setting, it could be an effective treatment option in a surgical environment (69).

Trying to reach a conclusion on the use of antipsychotics in preventing or treating delirium at this moment in time is impossible. Although the current body of evidence indicates that the use of antipsychotics in non-critically ill elderly patients yields better results than on the critically ill, both regarding the outcomes and the safety profile, with second generation antipsychotics being at least as efficacious as haloperidol and more safe, the matter still stands under a shadow of a doubt. As long as there are Cochrane reviews that state the data on this topic is of poor quality and the safety profile could not be properly assessed because the adverse effects were poorly or rarely reported (56), the use of antipsychotics in postoperative delirium should be done sagaciously using a “start low and then go slow” attitude.

**C) Sleep cycle altering medication**

The diurnal dysregulation or melatonin dysregulation is one of the current leading hypothesis when it comes to the pathogenesis of delirium. Sleep deprivation has long been linked to the development of delirium. Melatonin has been demonstrated to play a major role with its chronobiologic, sleep-wake cycle regulation, antioxidant and antiapoptotic, anti-inflammatory, anti-nociceptive and analgesic effects and its ability to prevent the hyperphosphorylation of the tau protein (14). Knowing all this, it was only natural to try this avenue in preventing or treating delirium. The results, unfortunately, have been met with mixed results. A recent meta-analysis conducted by Chen et al. included 189 medical patients and 480 surgical patients from 4 randomized control studies and came to the conclusion that no differences were found in the incidence of delirium between the two groups...
(melatonin intervention vs control) in the elderly patients that were presented to surgical wards (70). What is important and interesting to note is that regarding the medical patients there was a statistically significant reduction of 75% in the incidence of delirium. Also, one of the studies on surgical patients included in the analysis reported a decrease of the long-lasting episodes of delirium (>2 days) in the melatonin group. This conclusion should not be taken at face value, as the meta-analysis was marred by a high heterogeneity and lack of uniformity in the diagnostic criteria of delirium in the surgical studies subgroup analysis. The authors state that the small sample might not be consistent with the clinical practice and advise caution before applying these results in clinical practice as there is a dire need of more trials to determine the exact effect of melatonin on surgical patients with delirium. Interestingly enough, another study conducted after Chen’s meta-analysis came to the conclusion that administration of melatonin significantly decreases the incidence of delirium after cardiac surgery, so the game is still on (71).

Ramelteon is a melatonin agonist and is regarded as having a sixfold and threefold higher affinity for melatonin receptors 1 and 2 (MT1 and MT2) respectively, when compared to melatonin in vitro (70). Despite its potency, it is less studied on preventing surgical delirium than melatonin. Two recent studies indicate that ramelteon is associated with a significant reduction in postoperative delirium incidence in both lung cancer surgery and pharyngolaryngectomy with esophagectomy surgery (72) (73). More evidence is needed though to draw a conclusion.

A new promising molecule is Suvorexant whose mechanism of action is by antagonizing the orexin receptors, orexin being one of the neuropeptides responsible for the state of wakefulness, thus promoting sleep. One recent study indicates that the Suvorexant intervention group reported significantly lower delirium incidence after coronary artery bypass grafting (CABG) surgery (74). Another study tried to see the effects of ramelteon and suvorexant combined on the incidence of postoperative delirium, but the results were inconclusive (73).

When it comes to delirium treatment with melatonin or ramelteon, data is of low quality and comprised mostly of case reports or retrospective cohort studies. There are more articles on ramelteon than melatonin as a treatment for delirium and these seem to indicate a reduction both in the severity and the duration of delirium (75). This lead looks promising but is in dire need of more statistically-oriented evidence.

Other aspects worth studying in further trials are the effects of melatonin /ramelteon in preventing the different subtypes of delirium (hypoactive, hyperactive and mixed) and the effects of different doses of melatonin/ramelteon in preventing delirium. When it comes to the first aspect, it has been shown that urinary excreted 6-SMT (6-sulfatoxymelatonin) is higher in hypoactive delirium and lower in hyperactive delirium (76) so it could well be that the different subtypes of delirium might respond differently to the administration of melatonin. Regarding the second aspect, a higher dose of melatonin might inhibit the endogenous melatonin secretion through a negative feedback mechanism (77).

D)Cholinesterase Inhibitors

Low Acetylcholine has been linked to delirium (14). By inhibiting its degradation and consecutively improving the amount found in the synaptic space, it has been theorised that cholinesterase inhibitors can prevent delirium and slow the progression of dementia. Rivastigmine and Donepezil are two of the most studied drugs of this class. Data on Rivastigmine is conflicting. When it comes to preventing postoperative delirium, one study showed no significant difference in reducing its incidence (rivastigmine intervention vs control) in elective cardiac surgery (78), while another study conducted on a hip fracture surgery population with preexisting cognitive impairment stated that rivastigmine reduced both the incidence and the mean severity of delirium (79).

The scarce data on Donepezil does not seem to support this drug at the moment. One study on an elderly hip fracture group found no significant reduction on postoperative delirium incidence and the intervention group experienced significantly more side effects compared to the control (80). Another study conducted on elective hip replacement patients also found no statistically significant reduction in delirium incidence, but the authors stated that there had been a consistent trend suggesting a possible benefit (81). It is important to note that both studies had small sample populations and that the acute setting of the first study vs the chronic one of the second can seriously impair drawing a conclusion on the matter at hand.

There is currently insufficient evidence derived from controlled trials suggesting that either Rivastigmine or Donepezil could be effective in treating postoperative delirium (82) (83).

E)Anesthetics

Cerebral hypoperfusion in the frontal, temporal and occipital cortex as well as in the thalamus and basal ganglia has been associated with postoperative delirium (84). Low cerebral blood flow is present in anesthesia induced by both intravenous propofol and volatile general anaesthetics like Sevoflurane, Desflurane and Isoflurane. A 2018 Cochrane Database Systematic Review could not draw a clear conclusion whether intravenous anaesthesia maintenance is better than the inhalational one at preventing delirium (85). Still, taking into consideration the low grade evidence, they found no difference in the incidence of postoperative delirium between the different volatile anaesthetic maintenance agents. On the other hand, they found low grade evidence that maintenance with propofol based total intravenous anaesthesia may reduce postoperative delirium rates. Another recent study not included in the aforementioned review found that a higher incidence of postoperative delirium was present in the Desflurane group compared to the Isoflurane one in older surgical patients (86). A multicenter, open-label, randomised controlled trial on 1200 elderly patients undergoing cancer surgery is underway and is studying the impact of inhalational vs intravenous anaesthesia on early delirium and long-term survival (87).

F)Pain management

Pain is another important factor implicated in the emergence of postoperative delirium and more so, it is possible to be influenced. A systematic review on the topic of pain management for hip fracture found only nerve blocks to be effective in reducing the incidence of
postoperative delirium and qualified it as a moderate strength of evidence. There was insufficient evidence on preventing delirium through pain-management with spinal anaesthesia alone, in continuous administration through a spinal catheter, or in conjunction with other medications such as morphine (88).

**G) Dexmedetomidine**

This is a drug that has sedative, anxiety reducing and pain decreasing effects through its highly selective alpha2-adrenergic agonistic action. It induces sedation by lowering the activity of noradrenergic neurons in the locus ceruleus and tuberomammillary nucleus, thereby increasing the activity of inhibitory GABA neurons in the ventrolateral preoptic nucleus (89). Although the use of dexmedetomidine has had mixed evidence regarding its efficacy in preventing delirium in surgical non-ICU patients, two recent 2018 meta-analyses shed light on the matter and be in accord that its perioperative administration can reduce delirium rates in both cardiac and non-cardiac surgical patients (90) (91). More studies are needed to determine the optimal dosage, safety profile (it might increase the rate of bradycardia) and timing, as one paper stated that intraoperative infusion in major elective non-cardiac surgery did not significantly reduce the incidence of delirium compared to placebo (92).

**ENDING NOTES**

The topic of postoperative delirium is far from being over-researched. On the contrary, it can be stated that, in fact, too few people (medical staff, healthcare management and family members alike) know of this entity. A common, united effort of all medical and surgical specialists involved is needed to spread the knowledge on the topic and further the current research on all levels – basic sciences, translational and clinical.

**REFERENCES:**

87. Kinjo S, Lim E, Magsaysay MV, Sands LP, Leung JM; Perioperative


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