Prevalência e Abordagem do *Delirium* em Doentes de Cuidados Paliativos em Regime de Internamento *versus* em Regime Domiciliário

Prevalence and Management of Delirium in Inpatient and Home-Based Palliative Care Patients

Rute Brás-Cruz[1] ⓘ, Teresa P. Medeiros[1], Maria Céu Rocha[2] ⓘ, Hugo Oliveira[2]

Resumo:

Introdução: O *delirium* é uma das complicações mais frequentes em cuidados paliativos com uma prevalência de 88% nos dias que precedem o fim de vida. Os dados sobre *delirium* no seguimento domiciliário em cuidados paliativos são escassos. O objetivo deste trabalho é caracterizar a população seguida por uma equipa de cuidados paliativos em regime intra-hospitalar e domiciliário, avaliar a prevalência de *delirium*, a estratégia terapêutica, o tempo de resolução e os fatores que se associam a maior ou menor prevalência de *delirium*.

Métodos: Foi realizado um estudo de coorte retrospetivo, que incluiu todos os doentes acompanhados no hospital e no domicílio por uma equipa de cuidados paliativos em Portugal durante o ano de 2019.

Resultados: Foram incluídos 496 doentes, dos quais 308 (62,1%) tiveram acompanhamento intra-hospitalar. Identificado *delirium* em 112 (22,6%) doentes e o fármaco de primeira linha foi o haloperidol (n = 58, 51,8%). Registaram-se 283 (57,1%) óbitos e a ocorrência de óbito foi significativamente maior naqueles que desenvolveram *delirium* (72,3%, *p* <0,001). Foram associadas a uma maior incidência de *delirium* o seguimento intra-hospitalar (27,9%, *p* <0,001), infeção (53,9%, *p* <0,001), alterações endócrinas (84,6%, *p* <0,001) e iónicas (55,0%, *p* <0,001), o uso de anticolinérgicos (54,1%, *p* = 0,001), antipsicóticos (42,6%, *p* = 0,031), corticosteroides (37,7%, *p* = 0,008) e a presença de metastização cerebral (50,0%, *p* = 0,046).

Conclusão: Existe uma prevalência significativa de *delirium* em doentes em fim de vida, sendo este um preditor de mau prognóstico. A implementação de cuidados paliativos de qualidade com uma abordagem multidisciplinar pode proporcionar um controlo mais eficaz do *delirium* e reduzir sua prevalência geral.

Palavras-chave: Cuidados Paliativos; Delírio

Abstract:

Introduction: Delirium is one of the most frequent complications in palliative care with a prevalence as high as 88% in the days preceding the end-of-life. Data on delirium home-based palliative care are scarce. The aim of this work is to characterize the population followed by a palliative care team, both in-hospital and at home, to assess the prevalence of delirium, the therapeutic strategy, its resolution, and the factors associated with the higher or lower prevalence of delirium.

Methods: A retrospective cohort study was carried out, including all patients followed in the hospital and at home by a palliative care team in Portugal during the year of 2019.

Results: A total of 496 patients were included, of whom 308 (62.1%) had in-hospital follow-ups. Delirium was identified in 112 (22.6%) of all patients and the first line drug used was haloperidol (51.8%). A total of 283 (57.1%) patients died, of whom 81 (28.6%) developed delirium. The occurrence of death was significantly higher in those who developed delirium (72.3%, p <0.001). Associated with higher incidence of delirium were identified in-hospital follow-up (27.9%, p <0.001), infection (53.9%, p <0.001), endocrine (84.6%, p <0.001) and ionic changes (55.0%, p <0.001), use of anticholinergics (54.1%, p = 0.001), antipsychotics (42.6%, p = 0.031), corticosteroids (37.7%, p = 0.008), and presence of brain metastasis (50.0%, p = 0.046).

Conclusion: There is a significant prevalence of delirium in end-of-life patients, which is a predictor of poor prognosis. The implementation of quality palliative care with a multidisciplinary approach may provide more effective control of delirium and reduce its overall prevalence.

Keywords: Delirium; Palliative Care.

Introduction

Delirium is one of the most frequent neuropsychiatric complications not only in critically ill patients, where it is traditionally discussed, but also in the context of palliative care. Despite the recognition of its existence, it was vaguely described until the 1990s, when the formal definition appears in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM).[1] Currently, and according to the fifth edition of

the DSM, delirium is a complex clinical syndrome that arises in the context of acute neurological dysfunction, characterized by a disturbance of attention, cognition, perception, and orientation over a short period of time with fluctuating severity during the course of a day.[2] This definition overlaps with the one established by the World Health Organization in the 11th edition of the International Classification of Diseases (ICD-11), where components of the sleep-wake cycle are added, such as reduced arousal of acute onset or total sleep loss with reversal of the sleep-wake cycle.[3]

From this definition, three subtypes of delirium were described according to the type of psychomotor activity: hyperactive, hypoactive, and mixed delirium.[4] Hyperactive delirium, characterized by restlessness, agitation, hallucinations, and refusal to cooperate with care, is the most easily identified, but it corresponds to only 25% of cases. The remaining percentage of patients with delirium show characteristics of hypoactive delirium5 with prostration, speech slowness, and apathy or with overlapping characteristics of hyper and hypoactivity, configuring a mixed delirium.[6] Precisely because it is more difficult to diagnose and often confused with fatigue, depression, or dementia,[2] hypoactive delirium is associated with a worse prognosis.

Although its pathophysiology is not yet fully understood, its etiology is usually multifactorial and each individual with delirium has a unique set of underlying causes that contribute to the symptoms,[1] a situation that is invariable in advanced disease in the context of palliative care. Advanced age, existence of critical illness, low functionality, and the presence of cognitive, visual or auditory disturbances are described as predisposing risk factors.[7] Precipitating risk factors for delirium7 include polymedication, the load of anticholinergics, drug intoxication, the presence of catheters, infection, dehydration, ionic changes such as hyponatremia and hypercalcemia, hypoxia, endocrine and metabolic disorders, organ dysfunction, paraneoplastic syndromes and the physical restraint itself.[8]

Little information is available on delirium in palliative care. Studies point to a prevalence of delirium of 8.4% in inpatient palliative care, increasing to 35% when delirium and/or descriptions suggestive of delirium are considered9 and up to 88% in the hours to days preceding the end of life.[10] Data on delirium in the follow-up of patients in palliative care at home are even more scarce and, despite being well described, this condition is still poorly recognized and treated in a less structured way.[5] In addition to its high prevalence, delirium plays a significant role in health care1 and its diagnosis should be valued as a predictor of poor prognosis and addressed to identify and correct potentially reversible factors.

This work aims to expand the existing information on delirium in palliative care both in-hospital and at home.

Our objective was to characterize the population followed by the Palliative Care Team of the Local Health Unit of Matosinhos (ECP-ULSM) in the hospital and at home and to assess the prevalence of delirium in these patients, the factors associated with it, the therapeutic strategy used and the time of resolution.

Material and Methods

A retrospective cohort study that included all patients referred and followed up by the ECP-ULSM in-hospital and at home between January 1st and December 31st, 2019. The necessary information was obtained by consulting the electronic medical record. The study was carried out in line with the recommendations of the Declaration of Helsinki of the World Medical Association. All data was anonymized and being a retrospective analysis of deceased patients, consent has been waived. The development or not of delirium or suggestive symptoms such as memory deficit, apathy, hallucinations, mood disturbances, fluctuation in the state of consciousness, persistent agitation6 and delirium prodromes such as changes in the sleep-wake cycle, irritability, and anxiety were recorded. Delirium was assumed whenever it had been identified as a problem in the palliative care team's records - no formal scale was used. The presence of predisposing factors and the presence of precipitating factors such as the existence of neoplasm or brain metastases, the use of drugs such as benzodiazepines, opioids, anticholinergics, quinolones and corticosteroids, ionic and endocrine changes - namely in blood glucose or thyroid function - were also recorded. In addition, information was collected on medication implemented for first and second line management of delirium, on its resolution, and time to resolution.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS® software, version 23 (IBM, Armonk, NY). Except for age (continuous variable) which is presented as mean +/- standard deviation, all other variables are categorical and, therefore, are presented as frequencies and percentages. The presence of association between categorical variables was analyzed using the Chi-square or Fisher test and the student's t test or the Mann-Whitney test was used to analyze continuous variables, following or not the normal distribution, respectively. Multivariate analysis consisted of binary logistic regression, including all variables associated with statistically significant differences in univariate analysis. A statistically significant difference was considered whenever the test value (p-value, p) did not exceed the 5% significance level ($p < 0.05$). Confidence intervals of 95% were used.

Results

DESCRIPTION OF THE POPULATION, PHARMACOLOGICAL TREATMENT, AND OUTCOMES

A total of 496 patients were included, 277 (55.8%) of whom were male, with a mean age of 74 (±13) years. Of these, 308 (62.1%) patients were followed up in the hospital and 188 (37.9%) were followed up at home. Delirium was identified in a total of 112 (22.6%) patients as described in Table 1.

Table 1: Demographic characteristics and incidence of delirium.

Variable	Population (n = 496)
Demographic characteristics	
Male gender	277 (55.8%)
Age (years)	74 (±13)
Delirium	112 (22.6%)
Follow-up	
In-hospital	308 (62.1%)
Delirium identification	86 (27.9%)
Home-based	188 (37.9%)
Delirium identification	26 (13.8%)

As for the pharmacological treatment of delirium, as shown in Table 2, the use of haloperidol, olanzapine, midazolam, risperidone and quetiapine as first and second line drugs was studied. The most commonly used first line drug was haloperidol (n = 58, 53.2%) with a statistically significant difference in the resolution of delirium (95.0%, p = 0.032). The drug that showed the lowest resolution was risperidone (40.0%, p = 0.018).

Table 2: First and second line treatment in patients with delirium.

First and second line treatment in patients with delirium	(n = 109)
haloperidol documented resolution	58 (53.2%) 95.0% (p = 0.032)
olanzapine documented resolution	2 (1.8%) 50.0% (p = 0.257)
midazolam documented resolution	17 (15.6%) 93.3% (p = 0.349)
risperidone documented resolution	5 (4.6%) 40.0% (p = 0.018)
quetiapine documented resolution	19 (17.4%) 84.2% (p = 0.509)
quetiapine documented resolution	8 (7.3%) 87.5% (p = 0.697)

From the population of 109 patients in whom delirium was identified and pharmacologically treated, resolution was documented in a total of 98 (89.9%) patients, the majority of those in less than 5 days (n = 80, 81.6%), with 39 (35.8%) patients requiring a second line drug. Table 3 describes the second line drugs used. The most chosen second line drug was

haloperidol (n = 13, 33.3%), followed by quetiapine (n = 11, 28.2%) which showed higher resolution as a second line drug (100.0%, p = 0.047) as can be seen in Table 3. There were no statistically significant differences between the use of a given pharmacological treatment and the time of resolution both in first line (haloperidol p = 0.289) and second line (quetiapine p = 0.573) therapy.

Table 3: Second line treatment used in patients with delirium.

Second line treatment	(n = 39)
haloperidol documented resolution	13 (33.3%) 61.5% (p = 0.115)
olanzapine documented resolution	1 (2.6%) 100.0% (p = 0.769)
midazolam documented resolution	10 (25.6%) 81.8% (p = 0.501)
risperidone documented resolution	0 (0.0%) 0.0%
quetiapine documented resolution	11 (28.2%) 100.0% (p = 0.047)
quetiapine documented resolution	4 (10.3%) 50.0% (p = 0.223)

A total of 283 (57.1%) patients died, of whom 81 (28.6%) developed delirium. The occurrence of death was significantly higher in patients who developed delirium, compared to those who did not (72.3% vs 52.6%; p <0.001). Of the patients evaluated at home and who died in 2019 (149 patients), 55 (36.9%) died in the hospital and 87 (58.3%) died at home. The prevalence of delirium was higher in patients who died at home (19.5%) compared to those who died in the hospital (7.3%).

Table 4: Characterization of delirium incidence and place of death.

Death	Population (n = 283)
Delirium incidence (regardless of follow-up)	81 (28.6%)
Follow-up at home a) death at home delirium identification b) death in hospital delirium identification	149 (52.6%) 87 (58.3%) 17 (19.5%) 55 (36.9%) 4 (7.3%)

Variable	Population (n = 496)
Delirium Outcome: death	112 (22.6%) 81 (72.3%; p <0.001)
Without delirium Outcome: death	384 (77.4%) 202 (52.6%; p <0.001)

VARIABLES THAT INFLUENCE THE PRESENCE OF DELIRIUM

From all the 496 patients included in the study, the variables previously identified as precipitating risk factors were studied, and the following were significantly associated with a higher incidence of delirium: in-hospital follow-up (27.9% *vs* 13.8%; *p* <0.001), infection (53.9% *vs* 19.6%; *p* <0.001), endocrine changes (84.6% *vs* 28.3%; *p* <0.001), ionic changes (55.0% *vs* 25.5%; *p* <0.001), antipsychotics (42.6% *vs* 28.0%; *p* = 0.031), corticosteroid therapy (37.7% *vs* 24.8%; *p* = 0.008), use of anticholinergics (54.1% *vs* 27 .5%; *p* = 0.001), presence of brain metastasis (50.0% *vs* 29.0%; *p* = 0.046). None of the other variables studied showed statistically significant differences.

Table 6: Multivariate analysis to adjust for confounding factors on the incidence of delirium.

Variable	OR	CI 95%	*p*-value
Hospital follow-up	3.3	1.75-6.29	*p*<0.001
Presence of infection	1.8	0.98-3.36	*p*=0.062
Endocrine changes	5.5	1.11-27.78	*p*=0.036
Electrolyte imbalance	1.3	0.65-2.55	*p*=0.471
Use of antipsychotics	2.4	1.19-4.78	*p*=0.014
Use of corticosteroids	1.6	0.93-2.63	*p*=0.087
Use of anticholinergic	1.8	0.82-3.95	*p*=0.148
Presence of brain metastasis	2.2	0.75-6.41	*p*=0.148

Table 5: Analysis of the contribution of variables in the incidence of delirium.

Variable	Delirium	Without delirium	*p*-value
Endocrine changes	84.6%	28.3%	*p* <0.001
Ionic changes	55.5%	25.5%	*p* <0.001
Use of anticholinergics	54.1%	27.5%	*p* = 0.001
Use of antipsychotics	42.6%	28.0%	*p* = 0,031
Use of corticosteroids	37.7%	24.8%	*p* = 0.008
Organ dysfunction	16.7%	23.6%	*p* = 0.194
Presence of neoplasm	23.1%	21.3%	*p* = 0.681
Presence of infection	53.9%	19.6%	*p* <0.001
Presence of brain metastasis	50.0%	29.0%	*p* = 0.046
In-hospital follow-up	27.9%	13.80%	*p* <0.001
Type of inpatient nursery	23.1%	29.6%	*p* = 0.270
Gender	25.3%	19.2%	*p* = 0.107
Dementia	30.1%	30.1%	*p* = 0.994
Depressive syndrome	35.4%	28.2%	*p* = 0.184
Use of antidepressants	27.0%	31.4%	*p* = 0.398
Use of benzodiazepines	29.6%	30.5%	*p* = 0.842
Use of opioids	32.0%	26.2%	*p* = 0.255
Use of quinolones	100.0%	29.9%	*p* = 0.127

PREDICTORS OF DELIRIUM

In a multivariate analysis, to adjust for confounding factors, in-hospital follow-up (OR=3.30; 95%CI = 1.75-6.29, *p* <0.001), the existence of endocrine changes (OR=5.50; 95%CI=1.11-27.78, *p* = 0.036) and the use of antipsychotics (OR=2.38; 95%CI=1.19-4.78, *p* = 0.014) were associated with a higher incidence of delirium.

Discussion

DELIRIUM IDENTIFICATION

Delirium is frequently associated with precipitating events that are often reversible, such as infection, dehydration and ionic changes superimposed on underlying vulnerability in the context of advanced disease,[11] which is why it is extremely important to look for and identify these changes. This premise is

valid not only in an inpatient context, but also in home follow--up. By allowing the family to identify symptoms suggestive of delirium, early recognition and treatment by the care team are possible, avoiding the need for emergency services and possible hospitalization. Of the 188 patients followed at home, delirium was identified in 26 (13.8%) patients, a value significantly lower than that identified in the in-hospital regimen (27.9%), and which was mostly managed at home.

In the 112 patients diagnosed with delirium, some factors were found to be associated with a higher incidence of this problem, such as: in-hospital follow-up (OR=3.30; 95%CI=1.75-6.29, *p* <0.001), which may be overestimated since difficult-to-manage delirium or terminal restlessness may be the reason for hospitalization or because it is more easily identified by the various health professionals; the existence of identified and corrected endocrine changes (OR=5.50; 95%CI=1.11-27.78, *p* = 0.036); and the use of antipsychotics (OR=2.38; 95%CI=1.19 -4.78, *p* = 0.014), possibly due to the presence of patients with prior changes in behavior that were medicated with these drugs.

DELIRIUM TREATMENT

Patients may be agitated without delirium (i.e., without disturbances of consciousness or cognition) for a variety of reasons, such as fecal impaction, urinary retention, uncontrolled pain or drug-induced akathisia, so it is important to know the diagnostic criteria for delirium and address any possible confounding factors.[12] For this reason, not all patients with delirium (n = 112) underwent pharmacological therapeutic intervention (n = 109).

There is little research on non-pharmacological prevention and only a limited number of trials on pharmacological therapy in delirium.[13] Thus, evidence for the use of antipsychotics in the treatment of delirium is also quite limited and the existing literature is often contradictory. A Cochrane review by Anne M. Finucane et al on drug therapy for delirium in terminally ill patients concluded that, based on this one study and with a small sample size, haloperidol is the most suitable drug for the treatment of patients with end-of-life delirium, with chlorpromazine being an acceptable alternative.[14] The National Institute for Health and Care Excellence (NICE) guidelines[15] recommend the use of haloperidol if the patient poses a danger to himself or others when non-pharmacological interventions have failed. In contrast, the European Society for Medical Oncology (ESMO)[16] guidelines advise against the use of haloperidol and risperidone in cancer patients with end-of-life delirium, although there is some evidence of benefit in the use of olanzapine and quetiapine.

Of all the drugs studied, the most used was haloperidol (53.2%), perhaps because of the ease of administration in the hospital environment (intramuscular route) and at home (orally) and because of the team's own experience. However, in this sample, the data presented show greater resolution associated with the use of haloperidol, which is why it was

also the drug of choice in a greater number of second line cases (33.3%). There may be a role for quetiapine as a second line drug, since it was associated with resolution of delirium 100.0% of the cases with a statistically significant difference (*p* = 0.047), which is in agreement with the existing literature described above.[14-16]

Despite this, it must be taken into account that non-pharmacological measures and the prevention of delirium come first, and the use of drugs should be reserved for cases where prevention has not been effective and where non-pharmacological therapy has failed.

The main goal of delirium management in the context of palliative care, given its poor prognosis, should be to prioritize the comfort of the patient,[2] the tranquility of the care team and the informed involvement of family members and caregivers.

RESOLUTION OF DELIRIUM

According to the literature,[17] the duration of delirium can vary widely, from a few days - in most patients - to weeks or months. In the latter case, the diagnosis of persistent delirium is assumed. The more effective the prevention and the earlier the diagnosis, the easier and faster the resolution. Although not using a standard scale, delirium was described as solved in most patients observed by ECP-ULSM in less than 5 days. However, in the study population, the use of the above-mentioned drugs did not influence the time to resolution of delirium in patients treated in the hospital or at home.

DELIRIUM AS A PREDICTOR OF DEATH

In palliative care, delirium is interpreted as a sign of imminent death and, in this context, the anguish felt by patients, family members and caregivers is generally aggravated by the difficulty in communication and the difficulty controlling behavioral changes.[18] This premise is described in terminal patients in days to weeks, mainly in those diagnosed with advanced cancer[2] in palliative care units and in hospice facilities.

Hospital mortality of elderly people with delirium ranges from 22% to 76%.[19] Consistent with this evidence, the outcome of death was also higher in patients who developed delirium compared to those who did not, with statistical significance (72.3% *vs* 52.6%; *p* <0.001).

Despite the confirmation of delirium as a predictor of death, this does not mean that death will occur in the hospital. Of all the patients followed at home and who died, the identification of delirium was higher in those who died at home (19.5%) compared to those who died in the hospital (7.3%). We must note that for this study it was also included suggestive symptoms of delirium. In the end of life can be very challenging for the home-care palliative team the interpretation given by the family. But with the early identification of this disorder and the involvement of the family in its management, it was possible for the patient with delirium to followed at home to die at home.

LIMITATIONS

Despite presenting and studying a significant sample of patients (n = 496), the diagnosis of delirium was not applied according to standardized scales for this purpose, but rather assumed based on the records made by the ECP-ULSM, so there is an assumed identification bias. Underdiagnosis of hypoactive delirium and overdiagnosis of hyperactive delirium are also assumed, the latter tending to be more recognized in general wards and aggravated by the greater use of physical restraint measures and the more frequent use of haloperidol in this context.

Conclusion

This study demonstrates the non-negligible prevalence of delirium in end-of-life patients, especially in an in-hospital context, as well as its secondary causes and its value as a predictor of poor prognosis. Due to the multifactorial nature of delirium in the context of palliative care, a multidisciplinary approach that can predict and correct its precipitating factors, as well as the early implementation of quality home and in-hospital palliative care at the end of life, may provide more effective control of delirium and reducing its overall prevalence. ∎

Correspondence / Correspondência:

Rute Brás-Cruz – rutebcruz@gmail.com
Departamento de Medicina, Hospital Pedro Hispano – Unidade Local de Saúde de Matosinhos, Matosinhos, Portugal
Rua Dr. Eduardo Torres, 4464-513 Sra. da Hora, Matosinhos - Portugal

REFERENCES

1. Setters B, Solberg LM. Delirium. Prim Care. 2017;44:541-59. doi: 10.1016/j.pop.2017.04.010.
2. Bramati P, Bruera E. Delirium in palliative care. Cancers. 201;13:5893. doi: 10.3390/cancers13235893.
3. Organização Mundial da Saúde. ICD-11 for Mortality and Morbidity Statistics [Internet]. 2020. 2020 [accessed 2022 Aug 30]. Available at: https://icd.who.int/browse11/l-m/en. Available from: https://icd.who.int/browse11/l--m/en#/http%3A%2F%2Fid.who.int%2Ficd%2Fentity%2F897917531
4. Bush SH, Tierney S, Lawlor PG. Clinical Assessment and Management of Delirium in the Palliative Care Setting. Drugs. 2017;77:1623–43. doi: 10.1007/s40265-017-0804-3.
5. Marcantonio ER. Delirium in hospitalized older adults. N Engl J Med. 2017;377:1456–66. doi: 10.1056/NEJMcp1605501.
6. Recchia A, Rizzi B, Favero A, Nobili A, Pasina L. Prevalence of delirium in end-of-life palliative care patients: an observational study. Med Princ Pract. 2022;31:118-24. doi: 10.1159/000521994.
7. Wilson JE, Mart MF, Cunningham C, Shehabi Y, Girard TD, MacLullich AM, et al. Delirium. Nat Rev Dis Primers. 2020;6:90. doi: 10.1038/s41572-020-00223-4. Erratum in: Nat Rev Dis Primers. 2020;6:94.
8. Davis DHJ, Muniz-Terrera G, Keage HA, Stephan BC, Fleming J, Ince PG, et al. Association of delirium with cognitive decline in late life: a neuropathologic study of 3 population-based cohort studies. JAMA Psychiatry. 2017;74:244-51. doi: 10.1001/jamapsychiatry.2016.3423.
9. Rebelo CC, Oliveira H. Abordagem do Delirium na Comunidade. Gaz Med. 2021;8:263–73.
10. Portela Millinger F, Fellinger M. Clinical characteristics and treatment of delirium in palliative care settings. Memo - Mag Eur Med Oncol. 2021;14:48–52.
11. Watt CL, Momoli F, Ansari MT, Sikora L, Bush SH, Hosie A, et al. The incidence and prevalence of delirium across palliative care settings: A systematic review. Palliat Med. 2019;33:865–77. doi: 10.1177/0269216319854944.
12. Breitbart W, Alici Y. Agitation and delirium at the end of life: "We couldn't manage him". JAMA. 2008;300:2898-910, E1. doi: 10.1001/

jama.2008.885.

13. Featherstone I, Hosie A, Siddiqi N, Grassau P, Bush SH, Taylor J, et al. The experience of delirium in palliative care settings for patients, family, clinicians and volunteers: A qualitative systematic review and thematic synthesis. Palliat Med. 2021;35:988–1004. doi: 10.1177/02692163211006313.

14. Jackson KC, Lipman AG. Drug therapy for delirium in terminally ill patients. Cochrane Database Syst Rev. 2004:CD004770. doi: 10.1002/14651858. CD004770. Update in: Cochrane Database Syst Rev. 2012;11:CD004770.

15. National Clinical Guideline Center. DELIRIUM: diagnosis, prevention and management Update information. Clin Guidel 103 [Internet]. [accessed 2022 July]. Available at: Available from: www.nice.org.uk/guidance/cg103

16. Bush SH, Lawlor PG, Ryan K, Centeno C, Lucchesi M, Kanji S, et al. Delirium in adult cancer patients: ESMO Clinical Practice Guidelines. Ann Oncol. 2018;29:iv143–65. doi:10.1093/annonc/mdy147

17. Cole MG, Ciampi A, Belzile E, Zhong L. Persistent delirium in older hospital patients: a systematic review of frequency and prognosis. Age Ageing. 2009;38:19–26. doi: 10.1093/ageing/afn253.

18. Carlson B. Delirium in patients with advanced cancer. Lancet Oncol. 2016;17:e379. doi: 10.1016/S1470-2045(16)30380-1.

19. Bruera E, Miller L, McCallion J, Macmillan K, Krefting L, Hanson J. Cognitive failure in patients with terminal cancer: a prospective study. J Pain Symptom Manage. 1992;7:192–5.