FARMACI *OFF-LABEL* IN CURE PALLIATIVE (CP)

PER LA POPOLAZIONE ADULTA

Proposta di immissione nell'elenco dei medicinali istituito con la L. 648/96 di farmaci utilizzati ***off-label*** nell'ambito delle **Cure Palliative** (CP)

Tavolo Tecnico di Lavoro sull'uso dei farmaci per le Cure Palliative *off-label*

composto

dalla Società Italiana di Cure Palliative (SICP)

e dall'Agenzia Italiana del Farmaco

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Sommario

1. INTRODUZIONE

1.1. Utilizzo *off-label* dei farmaci in Cure Palliative

Si definisce *off-label* l'impiego di farmaci già registrati, ovvero disponibili al pubblico, usati in maniera non conforme a quanto previsto dal riassunto delle caratteristiche del prodotto. Una prescrizione *off-label* indica l'uso di un medicinale, per indicazione e/o via di somministrazione, dose, forma, diverso da quello approvato dalle agenzie regolatorie, AIFA in Italia, al momento della concessione dell'autorizzazione all'immissione in commercio[1]. Nelle Cure Palliative (CP) è una prescrizione motivata in vario modo: dall'assenza/carenza di studi clinici specifici nella popolazione da trattare pur essendo disponibili dati di efficacia in altre popolazioni di pazienti, dalla disponibilità di nuovi dati di efficacia e sicurezza non ancora recepiti in scheda tecnica, dalla mancanza di alternative terapeutiche valide ed efficaci[2]. Nella pratica medica si assiste ad una frequente prescrizione di farmaci *off-label* che sembra coinvolgere soprattutto alcuni gruppi di pazienti, bambini, anziani, persone alla fine della vita, per i quali spesso non vi è una efficace terapia approvata e nei quali, per ragioni legate a riconosciuta fragilità, la proposizione e conduzione di studi clinici, in particolare controllati randomizzati, risulta a tutt'oggi complessa[3-6].

Un recente studio canadese[7] ad esempio, rileva una frequenza di prescrizioni *off-label* dell'11%, per anticonvulsivanti, antipsicotici e antidepressivi. Un'indagine del 2006 condotta negli Stati Uniti dimostra che il 21% delle prescrizioni dei 160 farmaci più comuni risulta essere *off-label*. Ulteriori studi condotti dal 2005 al 2011 indicano come la prescrizione *off-label* sia diffusa in tutto il mondo e in vari settori della pratica medica: medicina generale (11%), psichiatria (8%), ostetricia, pediatria (fino al 89%), oncologia (fino al 65%), HIV/AIDS (fino al 40%) e cure palliative[2, 8].

Nel 2009 è stata condotta un'analisi osservazionale in alcuni hospice italiani (66 centri di cure palliative) che ha rilevato una prescrizione di farmaci *off-label* per indicazione del 4.5% di tutte le prescrizioni terapeutiche effettuate nel 25.2% dei pazienti, mentre l'uso *off-label* per via di somministrazione sottocutanea, non indicata in scheda tecnica, interessava l'85.4% di tutte le prescrizioni sottocute (escluse insulina ed eparina)[9].

L'impiego *off-label* dei farmaci presenta importanti risvolti clinici, legali ed etici e comporta, oltre all'assunzione di responsabilità diretta del medico prescrittore, in particolare per efficacia terapeutica e possibili modificazioni del rapporto rischio/beneficio, compartecipazione informata dei pazienti ed effetti sulla rimborsabilità. Questi limiti tuttavia non impediscono tale utilizzo dei farmaci.

Si tratta di un impiego giustificato da evidenze scientifiche e spesso anche da pratica consolidata. In alcuni casi, per questi motivi, è possibile l'inserimento del medicinale nell'elenco dei farmaci erogabili a carico del Servizio Sanitario Nazionale (SSN) istituito ai sensi della legge 648/96 oppure l'approvazione dai comitati etici, poiché si intende migliorare la pratica medica in attesa che, laddove possibile, si apportino modifiche opportune dell'autorizzazione all'immissione al commercio (AIC), processo lungo e complesso, che necessita di investimenti finanziari che le industrie farmaceutiche non sempre sono disposte a impegnare.

La prescrizione *off-label*, quindi, non significa inevitabilmente un'insufficiente evidenza scientifica per l'uso di un farmaco, ma a volte semplicemente un'insufficiente interesse all'ampliamento o al mantenimento dell'impiego. Nella realtà medica l'uso *off-label* è sempre più diffuso per tentare di trattare pazienti che non vedono soddisfatti i propri bisogni di cura con farmaci impiegati secondo convenzione ovvero AIC. Va ricordato a conferma di questa analisi che in UK vengono presentate alle Commissioni del National Health Service (NHS), circa 1000 richieste/anno di esame per impiego *off-label*[(b)]. Di fatto la prescrizione off-label è parte integrante della medicina contemporanea. In molti settori (oncologia, pediatria, geriatria, ostetricia) l'assistenza non può prescindere dall'uso *off-label* dei medicinali[(10)].

In cure palliative e in terapia del dolore, l'obiettivo principale è quello di alleviare la sofferenza, il dolore e i sintomi. I pazienti che si rivolgono ai centri specialistici vi arrivano dopo aver utilizzato numerosi farmaci che, nonostante l'impiego appropriato, non hanno portato beneficio alla loro malattia e sofferenza. Spesso sono portatori di patologie multiple, riferiscono sintomi complessi e devono essere trattati con molti farmaci contemporaneamente.

Il loro stato di salute, fragile e compromesso, tende a modificarsi molto rapidamente. In questo complesso contesto origina la necessità di prescrizione *off-label*, soprattutto per quanto riguarda la via di somministrazione (spesso questi pazienti non deglutiscono e non hanno un patrimonio venoso accessibile) e le indicazioni cliniche. In letteratura scientifica in merito all'impiego *off-label* in cure palliative si riporta che almeno l'11% dell'uso *off-label* si riferisca ad una via di somministrazione diversa da quella approvata e nella maggior parte dei casi si tratta di somministrazione per via sottocutanea o sublinguale. L'impiego *off-label* di farmaci, in particolare per via sottocutanea, è descritto in numerose pubblicazioni scientifiche[(7,9,10,14,22)].

Midazolam, aloperidolo, ioscina butilbromuro, metoclopramide, sono solo alcuni esempi di farmaci abitualmente utilizzati per questa via in tutte le nazioni in cui i farmaci sono disponibili al pubblico e sono attive le cure palliative[(9,10,12,13,15)]. Inoltre nel 2010 anche la European Association of Palliative Care (EAPC) ha emanato raccomandazioni in cui è fortemente raccomandato l'utilizzo della via sottocutanea per la somministrazione di farmaci, in particolare di oppioidi, nel paziente che non è in grado di assumerli per *os* o per via transdermica[(23)].

Va ricordato inoltre come in cure palliative un altro aspetto particolarmente importante nella somministrazione di farmaci è rappresentato dalla necessità di somministrare più farmaci contemporaneamente anche nella stessa infusione[(16-21)]. Sono dunque necessarie conoscenza, massima attenzione e aggiornamento in merito a compatibilità e stabilità delle soluzioni preparate oltre che alla loro compatibilità con i vari tipi di infusori utilizzati.

Tali conoscenze e informazioni devono essere parte integrante del bagaglio tecnico-scientifico del medico palliativista o terapista del dolore ed è necessario che tutti gli operatori sanitari possano accedere rapidamente alle informazioni, per mezzo di pubblicazioni, testi specifici o banche dati dedicate, di validità riconosciuta[(23)].

1.2. Farmaci *off-label* e Legge 648/96

In Italia, per alcuni farmaci, l'utilizzo *off-label* è disciplinato dalla Legge 648/96 che ha permesso di identificare una lista di farmaci con un'indicazione terapeutica diversa da quella autorizzata, ma impiegati nella pratica clinica in ragione dell'uso consolidato e sulla base di dati di letteratura scientifica. Questi farmaci, una volta inseriti nell'elenco dei medicinali istituito con la Legge 648/96, vengono somministrati sempre sotto diretta responsabilità del medico, ma possono essere rimborsati dal Servizio Sanitario Nazionale.

In questo elenco vi sono farmaci, che coprono parzialmente i bisogni prescrittivi delle diverse aree della medicina palliativa.

Nell'analisi dell'elenco mancano peraltro alcuni medicinali usati frequentemente per il controllo del dolore e degli altri sintomi nelle CP.

Data la peculiarità delle situazioni e gli obiettivi di cura che le CP si propongono, abbiamo individuato una lista di farmaci usati nelle CP per i quali l'inclusione nell'elenco dell'Agenzia Italiana del Farmaco (AIFA), istituito con la Legge 648/96, rappresenta per i pazienti, gli operatori e per tutto il sistema salute un obiettivo di efficacia, sicurezza ed equità.

1.3. Bibliografia

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Documenti disponibili su siti web

a. https://www.nice.org.uk/process/pmg14/chapter/introduction
b. http://www.aifa.gov.it/content/farmaci-label

Riferimenti normativi

Legge 648 23/12/1996 e successivi aggiornamenti
DM 11.02.1997 e successivi aggiornamenti

Legge n.94 08/04/1998

DM 08/05/2003 uso compassionevole
Legge finanziaria 2007 e 2008
Decreti Giunte Regionali

2. OBIETTIVO DEL LAVORO

Con questo documento sottoponiamo all'attenzione dell'AIFA un elenco di farmaci utilizzati *off-label* nelle CP e ritenuti essenziali per risolvere, almeno in parte, la difficile situazione di non disporre di medicinali studiati e approvati. Sono stati individuati **8 farmaci** che routinariamente, per specifiche indicazioni, nella pratica clinica delle CP, vengono utilizzati *off-label*, con modalità che differiscono da quelle per cui sono stati autorizzati in termini di indicazione terapeutica, via di somministrazione e formulazione.

I farmaci individuati sono:

- ALOPERIDOLO
- BUTILBROMURO DI JOSCINA
- DESAMETASONE
- GABAPENTIN
- METOCLOPRAMIDE
- MIDAZOLAM
- MORFINA solfato e MORFINA cloridrato
- OCTREOTIDE

3. METODOLOGIA

Al fine di derivarne una proposta di inserimento nella lista dei farmaci erogabili, il lavoro svolto comprende informazioni circa l'evidenza scientifica a supporto dell'uso *off-label* (dati di letteratura, RCT, uso consolidato nella pratica) e l'utilizzo del principio attivo nell'indicazione *off-label* in altri Paesi. È stato inoltre analizzato lo stato dell'arte relativo a precedenti richieste di inserimento nell'elenco dell'AIFA, istituito con la Legge 648/96.

La lista ha la finalità di indicare i principi attivi, per ciascuna classe ATC, che possano essere utilizzati nell'adulto nell'ambito delle CP, anche se il loro uso non è autorizzato. Per alcuni di essi si tratta di un utilizzo razionale in quanto supportato dalle evidenze disponibili, anche se non esistono a supporto del loro impiego formali studi registrativi, perché si tratta di molecole vecchie o per difficoltà oggettive nella conduzione di trial clinici in Cure Palliative.

Per ciascun principio attivo individuato è stata formalizzata una **scheda** in cui è indicata la **specifica indicazione** di **richiesta di autorizzazione** nella pratica clinica, il **razionale** della richiesta, le **evidenze** a supporto della richiesta (con l'*abstract* dei singoli lavori), eventuali **note aggiuntive**.

In allegato le tabelle riassuntive degli otto farmaci per i quali viene chiesto l'inserimento nell'elenco dei medicinali istituito con la Legge 648/96 e per i quali è prevista l'acquisizione del relativo consenso informato.

4. SCHEDE DEI SINGOLI FARMACI

4.1. ALOPERIDOLO, formulazione a rilascio immediato

USO *OFF-LABEL* CHE SI VUOLE AUTORIZZARE:

1. Somministrazione SC per **agitazione psicomotoria/delirio** per la fase avanzata di malattia (pazienti con aspettativa di vita presumibile < 3 mesi).
2. Somministrazione SC per il controllo **nausea e vomito e singhiozzo** in pazienti che necessitano di terapia sintomatica di supporto in fase avanzata di malattia (aspettativa di vita presumibile < 3 mesi).

RAZIONALE DELLA RICHIESTA:

1. **L'agitazione psicomotoria/delirium** è una delle più comuni complicazioni neuropsicologiche nei pazienti in fase avanzata di malattia e nei pazienti negli ultimi giorni di vita. La percentuale soggettiva in caso di delirium è fonte di sofferenza fisica e psichica, quindi un trattamento farmacologico palliativo trova numerose indicazioni. Crea inoltre problemi di gestione clinica e assistenziale, necessitando un trattamento farmacologico. Infatti il delirio è uno dei sintomi più frequenti nei pazienti che ricorrono alle cure palliative ed ha un pesante impatto sulla loro qualità della vita. Il farmaco di prima scelta è l'aloperidolo che presenta minori effetti sedativi, anticolinergici e cardiovascolari rispetto agli altri neurolettici; può essere somministrato per via orale, intramuscolare, endovenosa e sottocutanea.
2. La **nausea e il vomito sono comuni nei pazienti in fase avanzata** (aspettativa di vita presumibile < 3 mesi) di malattia e sono causa di profondo distress e impatto sulla loro qualità della vita. L'aloperidolo ha anche una potente attività antiemetica che lo rendono il farmaco di prima scelta nel trattamento di molte situazioni ricorrenti nel setting di cure palliative.

SITUAZIONE ATTUALE APPROVATA:

cp/gtt: agitazione psicomotoria, delirio, allucinazioni, singhiozzo, vomito

fl/ solo im: psicosi acuta, delirium e/o allucinazioni, alte dosi

RICERCA BIBLIOGRAFICA RICHIESTA 1:

Parole chiave: Aloperidolo, delirium, advanced cancer, terminally ill

Lavori evidenziati:

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Parole chiave: Aloperidolo, nausea and vomiting, terminal cancer patients.

Lavori evidenziati:

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NOTE:

L'aloperidolo di causa il prolungamento del tratto QT, ma è noto che questo effetto collaterale è dose dipendente (>35mg/d) solo quando somministrato per via endovenosa e in uno studio tale effetto è stato riscontrato in meno dell'11% dei casi. È difficile determinare il rischio cardiaco dell'aloperidolo e come estenderlo ai pazienti in fase terminale di malattia e con delirio. Peraltro il rischio di aritmie e alterazioni del QT sono associate spesso alla presenza di diversi fattori di rischio, in parte modificabili, che permettono di individuare i pazienti ad alto rischio per ottimizzare l'uso dell'aloperidolo per via endovenosa, come evidenziato in molti studi.

COMMENTI E CONCLUSIONI:

I dati a disposizione sono espressione della pratica clinica consolidata per i pazienti in cure palliative. La maggior parte degli articoli è frutto di studi retrospettivi e proviene da singole istituzioni, riportando esperienze di popolazioni selezionate di pazienti e raccolte in periodi temporalmente molto lunghi. Tuttavia le segnalazioni presenti in letteratura propongono l'utilizzo dell'aloperidolo in CP come farmaco efficace in situazioni quali l'agitazione psicomotoria, il delirio, l'ostruzione intestinale da carcinosi peritoneale maligna e la gestione di nausea e vomito nei pazienti con neoplasia in fase di terminalità, che non presentano alternative terapeutiche. L'attuale scheda tecnica del farmaco prevede inoltre il suo utilizzo esclusivamente per via intramuscolare, ma la via di somministrazione maggiormente utilizzata in letteratura e soprattutto in cure palliative, è quella sottocutanea ed endovena. La Determinazione AIFA del 11 giugno 2010 (G.U. del 21 giugno 2010, n.142) ha controindicato la somministrazione di aloperidolo per via endovenosa, sottolineando come il farmaco "*non deve essere somministrato per via endovenosa, in quanto la somministrazione endovenosa di aloperidolo è stata associata ad un maggiore rischio di prolungamento del tratto QT e di Torsione di punta*". I casi per cui questo provvedimento è stato giustificato riguardano pazienti affetti da patologie psichiatriche deceduti per morte improvvisa da QT lungo, trattati con dosaggi di aloperidolo fino a 240 mg/die. Questa determinazione ha di fatto reso impossibile l'impiego di aloperidolo anche in dosi più basse rispetto a quelle indicate nel provvedimento, non essendo più disponibile la formulazione di aloperidolo per via ev.

Tale situazione ha inevitabilmente delle implicazioni per il trattamento dei pazienti in cure palliative, ambito nel quale l'aloperidolo è ampiamente utilizzato, come detto in precedenza, in quanto esso rappresenta uno dei farmaci di prima scelta nel trattamento di agitazione psicomotoria/delirio, occlusione intestinale maligna, nausea e vomito nei pazienti con neoplasia in fase avanzata. Nella letteratura scientifica internazionale, è inoltre incluso nella lista dei farmaci essenziali in cure palliative.

Dal momento che l'uso in cure palliative non è un'indicazione riportata in scheda tecnica, considerando l'uso importante nella pratica clinica per i pazienti in tale ambito, sia per il controllo dei sintomi che per la via di somministrazione, si richiede che venga esaminato specificatamente tale utilizzo, limitatamente alla sola formulazione non a rilascio prolungato.

GESTIONE DEL SINTOMO DELIRIO da**:** PALLIATIVE CARE IN THE DEVELOPING WORLD PRINCIPLES AND PRACTICE - Eduardo Burera, MD; Liliana De Lima, MHA; Roberto Wenk, MD and William Farr, MD, 2010	
Step 1: Valutare il Paziente	• Mantenere un alto grado di sospetto e allerta. Usare strumenti di valutazione validati come il *MMSE, Clock-making, o la Memorial Delirium Assessment Scale.* Questi strumenti dovrebbero essere usati solo quando non vi sono segni evidenti di delirio e al solo fine di una diagnosi precoce. • Raccogliere informazioni dal paziente circa la tipologia di allucinazione (più spesso tattile che visiva) e ideazione non aderente alla realtà. I pazienti non forniscono di frequente e in modo volontario, informazioni circa questi sintomi. • Ricercare segni clinici di sepsi, tossicità da farmaci (anche oppiacei), disidratazione, alterazioni metaboliche, o altre cause organiche di delirio. • Prescrivere esami specifici, ad esempio controllo di emocromo, elettroliti, calcemia (con albuminemia), funzionalità renale Rx Torace, SpO_2 e tutti gli altri esami ritenuti indicati.
Step 2: Trattare le cause sottostanti	• **Tossicità da oppiacei**: ruotare gli oppiacei. • **Sepsi:** iniziare un trattamento antibiotico appropriato dopo discussione con il paziente e i familiari • **Farmaci**: sospendere tutti i farmaci che potenzialmente possono scatenare o peggiorare il delirio come: antidepressivi triciclici, benzodiazepine, alcuni antiemetici, antibiotici e cimetidina. • **Disidratazione**: se non è disponibile una via e.v., iniziare un ipodermoclisi, soluzione salina fisiologica a 60 - 100 ml/h, o in alternativa somministrare boli di 500 ml tre volte al giorno. • **Ipercalcemia**: trattare con bifosfonati. • **Ipossia**: se possibile, trattare le cause sottostanti e somministrare ossigeno. • **Tumori o metastasi cerebrali**: valutare steroidi ad alte dosi.
Step 3: Trattare i sintomi del delirio	• **Agitazione/Allucinazione**: Per trattare l'agitazione, iniziare Aloperidolo 2 mg solo per uso orale e sottocute ogni 6h e 2 mg ogni 1h po/sc secondo le necessità del paziente. Per il controllo rapido di agitazione severa, può rendersi necessario incrementare i dosaggi sino a 2 mg ogni 15 - 30 min sc/per os o secondo le necessità del paziente nella prima ora e ogni ora secondo le necessità del paziente, a seguire. È molto importante controllare velocemente il sintomo per prevenire il distress del paziente, dei familiari, del *caregiver* e dell'equipe. Appena il sintomo è controllato, ridurre il dosaggio alla minima dose efficace, il prima

	possibile. Quando si debba avviare l'infusione di aloperidolo o di altri farmaci antipsicotici (come la clorpromazina o la perfenazina), si raccomanda la consulenza di un medico palliativista o di uno psichiatra. In rare occasioni è richiesto un approccio aggressivo; in questi casi si consiglia l'infusione di midazolam 1 mg/h sc, aggiustando il dosaggio in base alla risposta clinica.
Step 4: Fornisci supporto ai familiari, al *caregiver* e alla equipe	• La confusione mentale e l'agitazione sono espressione di un disturbo neurologico, ma non sono necessariamente legati a discomfort per il paziente. La disinibizione è una delle componenti principali del delirio è può essere causa di due fenomeni stressanti. • Espressioni drammatiche intercorrenti, caratterizzate da smorfie e lamenti: I familiari potrebbero interpretare questi fenomeni come un aggravamento della situazione clinica piuttosto che semplicemente un aumento delle manifestazioni espressive del paziente. Ciò potrebbe indurre un aumentato e inappropriato ricorso a farmaci oppiacei o sedativi. • Richieste irragionevoli ai familiari e all'equipe (ad esempio: "Voglio andare a casa ora."). Se queste richieste non vengono prontamente esaudite, il paziente potrebbe divenire aggressivo. Deve essere spiegato in modo approfondito ai familiari che la richiesta è formulata e dettata dal delirio.

ABSTRACT RICHIESTA 1:

1. Jackson KC.

Delirium is a common disorder that often complicates treatment in patients with life-limiting disease. Delirium is described using a variety of terms such as agitation, acute confusional states, encephalopathy, organic mental disorders, and terminal restlessness. Delirium may arise from any number of causes, and treatment should be directed at addressing these causes. In cases where this is not possible, or does not prove successful, the use of drug therapy may become necessary. The primary objective of this review was to identify and evaluate studies examining medications used to treat patients suffering from delirium during the terminal phases of disease. We searched the following sources: MEDLINE (1966 to July 2003), EMBASE 1980 to July 2003), CINAHL (1982 to July 2003), PSYCH LIT (1974 to July 2003), PSYCHINFO (1990 to July 2003) and the Cochrane Library Volume 2, 2003) for literature pertaining to this topic. Prospective trials with or without randomization and/or blinding involving the use of pharmacological agents for the treatment of delirium at the end of life were considered.Two reviewers independently assessed trial quality using standardized methods and extracted data for evaluation. Outcomes related to both efficacy and adverse effects were collected. Thirteen potential studies were identified by the search strategy. Of these, only one study met the criteria for inclusion in this review. This study evaluated 30 hospitalized AIDS patients receiving one of three different agents: chlorpromazine, haloperidol, and lorazepam. Analysis of this trial found chlorpromazine and haloperidol to be equally effective. Chlorpromazine was noted to slightly worsen cognitive function over time but this result was not significant. The

lorazepam arm of the study was stopped early as a consequence of excessive sedation. The data from one study of 30 patients would perhaps suggest that haloperidol is the most suitable drug therapy for the treatment of patients with delirium near the end of life. Chlorpromazine may be an acceptable alternative if a small risk of slight cognitive impairment is not a concern. However, there is insufficient evidence to draw any conclusions about the role of pharmacotherapy in terminally ill patients with delirium, and further research is essential.

2. Candy B.

One trial met the criteria for inclusion. In the 2012 update search we retrieved 3066 citations but identified no new trials. The included trial evaluated 30 hospitalised AIDS patients receiving one of three agents: chlorpromazine, haloperidol and lorazepam. The trial under-reported key methodological features. It found overall that patients in the chlorpromazine group and those in the haloperidol group had fewer symptoms of delirium at follow-up (to below the diagnostic threshold using the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) and that both were equally effective (at two days mean difference (MD) 0.37; 95% confidence interval (CI) -4.58 to 5.32; between two and six days MD -0.21; 95% CI -5.35 to 4.93). Chlorpromazine and haloperidol were found to be no different in improving cognitive status in the short term (at 48 hours) but at subsequent follow-up cognitive status was reduced in those taking chlorpromazine. Improvements from baseline to day two for patients randomised to lorazepam were not apparent. All patients on lorazepam (n = 6) developed adverse effects, including oversedation and increased confusion, leading to trial drug discontinuation.

3. Caraceni A.

Delirium is a frequent complication in oncology. Its definition as a disorder of consciousness, attention, and cognition is useful to elaborate a rational framework of its pathophysiology and to interpret the role of different aetiological factors and therapeutic interventions. Many aetiologies and an interaction between risk and predisposing factors have been shown to contribute to most cases of delirium. A screening of potential aetiologies is always mandatory to benefit reversible cases. The palliative treatment of symptoms of delirium includes non-pharmacological, environmental, and preventive interventions and the use of haloperidol. If haloperidol fails to control delirium, sedation with other drugs can be necessary. Specific attention to the qualitative aspects of care and to the effect of delirium on family members should be given in the overall assessment of the patient in his or her cancer trajectory.

4. Centeno C.

Delirium in advanced cancer is often poorly identified and inappropriately managed. It is one of the most common causes for admission to clinical institutions and is the most frequently cited psychiatric disorder in terminal cancer. Diagnosis of delirium is defined as a disturbance of consciousness and attention with a change in cognition and/or

perception. In addition, it develops suddenly and follows a fluctuating course and it is related to other causes, such as cancer, metabolic disorders or the effects of drugs. Delirium occurs in 26% to 44% of cancer patients admitted to hospital or hospice. Of all advanced cancer patients, over 80% eventually experience delirium in their final days. In advanced cancer, delirium is a multifactorial syndrome where opioids factor in almost 60% of episodes. Delirium in such patients, excluding terminal delirium, may be reversible in 50% of cases. Providing adequate end-of-life care for a patient with delirium is the main challenge. The family needs advice and it is important to create a relaxing environment for the patient. The primary therapeutic approach is to identify the reversible causes of delirium. Some therapeutic strategies have been shown to be effective: reduction or withdrawal of the psychoactive medication, opioid rotation, and hydration. Haloperidol is the most frequently used drug, and new neuroleptics such as risperidone or olanzapine are being tested with good results. Methylphenidate has been used for hypoactive delirium.

5. Hui D.

PURPOSE OF REVIEW: Delirium is the most common and distressing neuropsychiatric syndrome in cancer patients. Few evidence-based treatment options are available due to the paucity of high quality of studies. In this review, we shall examine the literature on the use of neuroleptics to treat delirium in patients with advanced cancer. Specifically, we will discuss the randomized controlled trials that examined neuroleptics in the front line setting, and studies that explore second-line options for patients with persistent agitation. RECENT FINDINGS: Contemporary management of delirium includes identification and management of any potentially reversible causes, coupled with nonpharmacological approaches. For patients who do not respond adequately to these measures, pharmacologic measures may be required. Haloperidol is often recommended as the first-line treatment option, and other neuroleptics such as olanzapine, risperidone, and quetiapine represent potential alternatives. For patients with persistent delirium despite first-line neuroleptics, the treatment strategies include escalating the dose of the same neuroleptic, rotation to another neuroleptic, or combination therapy (i.e., the addition of a second neuroleptic or other agent). We will discuss the advantages and disadvantages of each approach, and the available evidence to support each strategy.

6. Lonergam

Delirium occurs in up to 30% of hospitalised patients and is associated with prolonged hospital stay and increased morbidity and mortality. Recently published reports have suggested that the standard drug for delirium, haloperidol, a typical antipsychotic that may cause adverse extrapyramidal symptoms among patients, may be replaced by atypical antipsychotics such as risperidone, olanzapine or quetiapine, that are as effective as haloperidol in controlling delirium, but that have a lower incidence of extrapyramidal adverse effects. To compare the efficacy and incidence of adverse effects of haloperidol with risperidone, olanzapine, and quetiapine in the treatment of delirium. The trials were identified from a search of the Specialized Register of the Cochrane Dementia and Cognitive Improvement Group on 7 August 2006 using the search terms:haloperidol or haldol or risperidone or risperdal* or quetiapine or seroquel* or olanzapine or zyprexa* or

aminotriazole or sertindole or leponex* or zeldox* or ziprasidone. Types of studies included unconfounded, randomised trials with concealed allocation of subjects. For inclusion trials had to have assessed patients pre- and post-treatment. Where cross-over studies are included, only data from the first part of the study were examined. Interrupted time series were excluded. Length of trial and number of measurements did not influence the selection of trials for study. Where indicated, individual patient data were requested for further examination. Two reviewers extracted data from included trials. Data were pooled where possible, and analysed using appropriate statistical methods. Odds ratios of average differences were calculated. Only ”intention to treat” data were included. Analysis included haloperidol treated patients, compared with placebo. Three studies were found that satisfied selection criteria. These studies compared haloperidol with risperidone, olanzapine, and placebo in the management of delirium and in the incidence of adverse drug reactions. Decrease in delirium scores were not significantly different comparing the effect of low dose haloperidol (< 3.0 mg per day) with the atypical antipsychotics olanzapine and risperidone (Odds ratio 0.63 (95% CI 10.29 - 1.38; p = 0.25). Low dose haloperidol did not have a higher incidence of adverse effects than the atypical antipsychotics. High dose haloperidol (> 4.5 mg per day) in one study was associated with an increased incidence of extrapyramidal adverse effects, compared with olanzapine. Low dose haloperidol decreased the severity and duration of delirium in post-operative patients, although not the incidence of delirium, compared to placebo controls in one study. There were no controlled trials comparing quetiapine with haloperidol. There is no evidence that haloperidol in low dosage has different efficacy in comparison with the atypical antipsychotics olanzapine and risperidone in the management of delirium or has a greater frequency of adverse drug effects than these drugs. High dose haloperidol was associated with a greater incidence of side effects, mainly parkinsonism, than the atypical antipsychotics. Low dose haloperidol may be effective in decreasing the degree and duration of delirium in post-operative patients, compared with placebo. These conclusions must be tempered by the observation that they are based on small studies of limited scope, and therefore will require further corroborating evidence before they can be translated into specific recommendation for the treatment of delirium.

7. Vella-Brincat J.

Haloperidol is one of 20 ’essential‘ medications in palliative care. Its use is widespread in palliative care patients. The pharmacology of haloperidol is complex and the extent and severity of some of its adverse effects, particularly extrapyramidal adverse effects (EPS), may be related to the route of administration. Indications for the use of haloperidol in palliative care are nausea and vomiting and delirium. Adverse effects include EPS and QT prolongation. Sedation is not a common adverse effect of haloperidol. It is important that palliative care practitioners have a comprehensive understanding of the indications, doses, adverse effects and pharmacology of haloperidol. This review is intended to address these issues. Haloperidol is widely used in the management of psychotic disorders in both the adult and child population. Haloperidol is considered the first choice therapy in the management of agitation associated with delirium in end of life care. There is randomized controlled trial evidence to support the use of haloperidol in management of delirium hospitalized adults with AIDs.

8. WHO

Haloperidol is widely used in the management of psychotic disorders in both the adult and child population. Haloperidol is considered the first choice therapy in the management of agitation associated with delirium in end of life care. There is randomized controlled trial evidence to support the use of haloperidol in management of delirium hospitalized adults with AIDs. Haloperidol is included in the EML as an antipsychotic both for children and adults.

9. Hui JR.

Neuroleptics are commonly used in the management of delirium. Limited information is available regarding the dosage requirements and efficacy of neuroleptics in the palliative care setting. We determined the type and dose of neuroleptic use by delirium subtype. The medical records of 99 inpatients with advanced cancer were reviewed retrospectively. The doses of different neuroleptics, expressed as haloperidol equivalent daily doses (HEDDs), were correlated with delirium recall, recalled delirium symptom frequency, and associated distress from the patients', family caregivers', nurses' and palliative care specialists' perspectives. Subtypes of delirium included hypoactive in 20 (20%), mixed in 66 (67%), and hyperactive in 13 (13%). The median HEDD was 2.5mg, interquartile range (Q1-Q3) 1-4.7 mg (mean 4.0+/-5.9 mg), and it was significantly higher in agitated and mixed delirium as compared with hypoactive delirium (P=0.008). The neuroleptic dose was low and appeared to be ineffective in preventing patient delirium recall, with 73 (74%) patients remembering their episode of delirium as distressing. HEDD did not correlate with delirium recall, recalled symptom frequency, or distress for patients and family caregivers. However, HEDD increased with nurses' distress related to patients' symptoms (disorientation to place P=0.002, disorientation to time P=0.008, delusions P=0.041, and agitation P<0.001), and palliative care specialists' distress related to patients' hallucinatory symptoms (P=0.006) and agitation (P=0.006). In this study, the administered neuroleptic dose was influenced more by health care professional distress than by delirium symptom frequency. Future studies should examine the efficacy of neuroleptic dose according to individual delirium symptoms.

10. Gagnon PR

PURPOSE OF REVIEW: The past few years have witnessed increased research into delirium treatment and related issues, leading to better management (e.g. improved detection) and better understanding of phenomenology and pathophysiology. Many treatment and prevention trials have been conducted. RECENT FINDINGS: Delirium phenomenology studies revealed that even subsyndromal presentations may bear a poor prognosis. Varied pathophysiology may lead to different delirium subtypes with implications for treatment, especially the hypoactive subtype, for which systematic neuroleptic treatment remains controversial. The high prevalence of delirium has led to improved use of validated instruments and better trials. Nonpharmacological interventions remain an essential step in delirium management and have yielded positive results, especially in prevention. Two trials of haloperidol prophylaxis identified reduced severity and duration of delirium in one and reduced incidence in the other. Trials comparing

haloperidol with atypical antipsychotics, mainly risperidone and olanzapine, found equal efficacy but more side effects with haloperidol. SUMMARY: Use of validated detection instruments is now standard procedure in both specialized clinical practice and research. Although haloperidol remains the mainstay of treatment, recent trials have begun to discriminate between the use of different agents and pharmacological approaches.

11. Bruera E

Approximately 50% of patients diagnosed with cancer die because of progressive disease. Psychotropic drugs are frequently used for the management of physical and psychosocial symptoms in these patients. Thalidomide, cannabinoids and melatonin are emerging agents for the management of cachexia. Psychostimulants have a defined role in the management of opioid-induced sedation. Haloperidol, tricyclic anti-depressants and newer anti-depressants also have an established role in the management of neuropsychiatric symptoms such as delirium or depression. Cancer patients present unique challenges for successful psychotropic therapy including older age, malnutrition, autonomic failure, borderline cognition, opioid and psychotropic therapy. A practical clinical approach which defines a specific target symptom, an outcome latency period, expected side effects, and reviews possible drug interactions, and frequent monitoring is outlined. Continued research is needed to further define the role of psychotropics in the management of the different physical and psychosocial symptoms in advanced cancer patients.

12. Grassi L.

Delirium is a complex but common disorder in palliative care with a prevalence between 13 and 88 % but a particular frequency at the end of life (terminal delirium). By reviewing the most relevant studies (MEDLINE, EMBASE, PsycLit, PsycInfo, Cochrane Library), a correct assessment to make the diagnosis (e.g., DSM-5, delirium assessment tools), the identification of the possible etiological factors, and the application of multicomponent and integrated interventions were reported as the correct steps to effectively manage delirium in palliative care. In terms of medications, both conventional (e.g., haloperidol) and atypical antipsychotics (e.g., olanzapine, risperidone, quetiapine, aripiprazole) were shown to be equally effective in the treatment of delirium. No recommendation was possible in palliative care regarding the use of other drugs (e.g., α-2 receptors agonists, psychostimulants, cholinesterase inhibitors, melatonergic drugs). Non-pharmacological interventions (e.g., behavioral and educational) were also shown to be important in the management of delirium. More research is necessary to clarify how to more thoroughly manage delirium in palliative care.

13. Bush SH

CONTEXT: Delirium is a highly prevalent complication in patients in palliative care settings, especially in the end-of-life context.OBJECTIVES: To review the current evidence base for treating episodes of delirium in palliative care settings and propose a framework for future development. METHODS: We combined multidisciplinary input from delirium

researchers and other purposely selected stakeholders at an international delirium study planning meeting. This was supplemented by a literature search of multiple databases and relevant reference lists to identify studies regarding therapeutic interventions for delirium. RESULTS: The context of delirium management in palliative care is highly variable. The standard management of a delirium episode includes the investigation of precipitating and aggravating factors followed by symptomatic treatment with drug therapy. However, the intensity of this management depends on illness trajectory and goals of care in addition to the local availability of both investigative modalities and therapeutic interventions. Pharmacologically, haloperidol remains the practice standard by consensus for symptomatic control. Dosing schedules are derived from expert opinion and various clinical practice guidelines as evidence-based data from palliative care settings are limited. The commonly used pharmacologic interventions for delirium in this population warrant evaluation in clinical trials to examine dosing and titration regimens, different routes of administration, and safety and efficacy compared with placebo.CONCLUSION: Delirium treatment is multidimensional and includes the identification of precipitating and aggravating factors. For symptomatic management, haloperidol remains the practice standard. Further high-quality collaborative research investigating the appropriate treatment of this complex syndrome is needed.

14. Candy B.

BACKGROUND: Delirium is a syndrome characterised by a disturbance of consciousness (often fluctuating), cognition and perception. In terminally ill patients it is one of the most common causes of admission to clinical care. Delirium may arise from any number of causes and treatment should be directed at addressing these causes rather than the symptom cluster. In cases where this is not possible, or treatment does not prove successful, the use of drug therapy to manage the symptoms may become necessary. This is an update of the review published on 'Drug therapy for delirium in terminally ill adult patients' in The Cochrane Library 2004, Issue 2 (Jackson 2004).OBJECTIVES: To evaluate the effectiveness of drug therapies to treat delirium in adult patients in the terminal phase of a disease.SEARCH METHODS: We searched the following sources: CENTRAL (The Cochrane Library 2012, Issue 7), MEDLINE (1966 to 2012), EMBASE (1980 to 2012), CINAHL (1982 to 2012) and PSYCINFO (1990 to 2012). SELECTION CRITERIA: Prospective trials with or without randomisation or blinding involving the use of drug therapies for the treatment of delirium in adult patients in the terminal phase of a disease.DATA COLLECTION AND ANALYSIS: Two authors independently assessed trial quality using standardised methods and extracted trial data. We collected outcomes related to efficacy and adverse effects. MAIN RESULTS: One trial met the criteria for inclusion. In the 2012 update search we retrieved 3066 citations but identified no new trials. The included trial evaluated 30 hospitalised AIDS patients receiving one of three agents: chlorpromazine, haloperidol and lorazepam. The trial under-reported key methodological features. It found overall that patients in the chlorpromazine group and those in the haloperidol group had fewer symptoms of delirium at follow-up (to below the diagnostic threshold using the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) and that both were equally effective (at two days mean difference (MD) 0.37; 95% confidence interval (CI) -4.58 to 5.32; between two and six days MD -0.21; 95% CI -5.35 to 4.93). Chlorpromazine and haloperidol were found to be no different in improving cognitive status in the short term (at 48 hours) but at subsequent follow-up cognitive status was reduced in those taking chlorpromazine. Improvements from baseline

to day two for patients randomised to lorazepam were not apparent. All patients on lorazepam (n = 6) developed adverse effects, including oversedation and increased confusion, leading to trial drug discontinuation. AUTHORS' CONCLUSIONS:There remains insufficient evidence to draw conclusions about the role of drug therapy in the treatment of delirium in terminally ill patients. Thus, practitioners should continue to follow current clinical guidelines. Further research is essential.

15. Ross DD.

In addition to pain, patients who are approaching the end of life commonly have other symptoms. Unless contraindicated, prophylaxis with a gastrointestinal motility stimulant laxative and a stool softener is appropriate in terminally ill patients who are being given opioids. Patients with low performance status are not candidates for surgical treatment of bowel obstruction. Cramping abdominal pain associated with mechanical bowel obstruction often can be managed with morphine (titrating the dosage for pain) and octreotide. Delirium is common at the end of life and is frequently caused by a combination of medications, dehydration, infections or hypoxia. Haloperidol is the pharmaceutical agent of choice for the management of delirium. Dyspnea, the subjective sensation of uncomfortable breathing, is often treated by titration of an opioid to relieve the symptom; a benzodiazepine is used when anxiety is a component of the breathlessness.

16. Bruera E.

During the past 10 years there have been major changes in the management of the most common symptoms of terminal cancer. Opioid agonists remain the mainstay in the management of cancer pain. Slow-release preparations are currently available for several of these agents. The increased use of opioids has led to the recognition of opioid-induced neurotoxic effects and to the development of effective adjuvant drugs and other strategies to counteract these side effects. A number of drugs are available for the management of symptoms of cachexia, including corticosteroids and progestational drugs. Prokinetic drugs, either alone or in combination with other agents such as corticosteroids, are highly effective in the treatment of chronic nausea. For patients with asthenia, it should first be determined whether there are any reversible causes; if not, corticosteroids and psychostimulants may diminish the symptoms. Haloperidol, other neuroleptics and benzodiazepines may be required to manage hyperactive delirium. Oxygen and opioids are effective in treating dyspnea, whereas there is limited evidence that benzodiazepines provide any relief of this symptom. More research on the assessment and management of these devastating clinical symptoms of cancer is badly needed.

RCT DISPONIBILI

1. HUI D.

IMPORTANCE:The use of benzodiazepines to control agitation in delirium in the last days of life is controversial. OBJECTIVE: To compare the effect of lorazepam vs placebo as an

adjuvant to haloperidol for persistent agitation in patients with delirium in the setting of advanced cancer. DESIGN, SETTING, AND PARTICIPANTS: Single-center, double-blind, parallel-group, randomized clinical trial conducted at an acute palliative care unit at MD Anderson Cancer Center, Texas, enrolling 93 patients with advanced cancer and agitated delirium despite scheduled haloperidol from February 11, 2014, to June 30, 2016, with data collection completed in October 2016. INTERVENTIONS: Lorazepam (3 mg) intravenously (n = 47) or placebo (n = 43) in addition to haloperidol (2 mg) intravenously upon the onset of an agitation episode. MAIN OUTCOMES AND MEASURES: The primary outcome was change in Richmond Agitation-Sedation Scale (RASS) score (range, -5 [unarousable] to 4 [very agitated or combative]) from baseline to 8 hours after treatment administration. Secondary end points were rescue neuroleptic use, delirium recall, comfort (perceived by caregivers and nurses), communication capacity, delirium severity, adverse effects, discharge outcomes, and overall survival. RESULTS: Among 90 randomized patients (mean age, 62 years; women, 42 [47%]), 58 (64%) received the study medication and 52 (90%) completed the trial. Lorazepam + haloperidol resulted in a significantly greater reduction of RASS score at 8 hours (-4.1 points) than placebo + haloperidol (-2.3 points) (mean difference, -1.9 points [95% CI, -2.8 to -0.9]; P < .001). The lorazepam + haloperidol group required less median rescue neuroleptics (2.0 mg) than the placebo + haloperidol group (4.0 mg) (median difference, -1.0 mg [95% CI, -2.0 to 0]; P = .009) and was perceived to be more comfortable by both blinded caregivers and nurses (caregivers: 84% for the lorazepam + haloperidol group vs 37% for the placebo + haloperidol group; mean difference, 47% [95% CI, 14% to 73%], P = .007; nurses: 77% for the lorazepam + haloperidol group vs 30% for the placebo + haloperidol group; mean difference, 47% [95% CI, 17% to 71%], P = .005). No significant between-group differences were found in delirium-related distress and survival. The most common adverse effect was hypokinesia (3 patients in the lorazepam + haloperidol group [19%] and 4 patients in the placebo + haloperidol group [27%]). CONCLUSIONS AND RELEVANCE: In this preliminary trial of hospitalized patients with agitated delirium in the setting of advanced cancer, the addition of lorazepam to haloperidol compared with haloperidol alone resulted in a significantly greater reduction in agitation at 8 hours. Further research is needed to assess generalizability and adverse effects.

2. Franken LG

Over 80% of the terminally ill patients experience delirium in their final days. In the treatment of delirium, haloperidol is the drug of choice. Very little is known about the pharmacokinetics of haloperidol in this patient population. We therefore designed a population pharmacokinetic study to gain more insight into the pharmacokinetics of haloperidol in terminally ill patients and to find clinically relevant covariates that may be used in developing an individualised dosing regimen. METHODS: Using non-linear mixed effects modelling (NONMEM 7.2), a population pharmacokinetic analysis was conducted with 87 samples from 28 terminally ill patients who received haloperidol either orally or subcutaneously. The covariates analysed were patient and disease characteristics as well as co-medication. RESULTS: The data were accurately described by a one-compartment model. The population mean estimates for oral bioavailability, clearance and volume of distribution for an average patient were 0.86 (IIV 55%), 29.3 L/h (IIV 43%) and 1260 L (IIV 70%), respectively. This resulted in an average terminal half-life of haloperidol of around 30 h. CONCLUSION: Our study showed that the pharmacokinetics of haloperidol could be adequately described by a one-compartment model. The pharmacokinetics in terminally ill

patients was comparable to other patients. We were not able to explain the wide variability using covariates.

3. Breitbart W

OBJECTIVE: The purpose of this study was to examine the efficacy and side effects of haloperidol, chlorpromazine, and lorazepam for the treatment of the symptoms of delirium in adult AIDS patients in a randomized, double-blind, comparison trial. METHOD: Nondelirious, medically hospitalized AIDS patients (N = 244) consented to participate in the study and were monitored prospectively for the development of delirium. Patients entered the treatment phase of the study if they met DSM-III-R criteria for delirium and scored 13 or greater on the Delirium Rating Scale. Thirty patients were randomly assigned to treatment with haloperidol (N = 11), chlorpromazine (N = 13), or lorazepam (N = 6). Efficacy and side effects associated with the treatment were measured with repeated assessments using the Delirium Rating Scale, the Mini-Mental State, and the Extrapyramidal Symptom Rating Scale. RESULTS: Treatment with either haloperidol or chlorpromazine in relatively low doses resulted in significant improvement in the symptoms of delirium as measured by the Delirium Rating Scale. No improvement in the symptoms of delirium was found in the lorazepam group. Cognitive function, as measured by the Mini-Mental State, improved significantly from baseline to day 2 for patients receiving chlorpromazine. Treatment with haloperidol or chlorpromazine was associated with an extremely low prevalence of extrapyramidal side effects. All patients receiving lorazepam, however, developed treatment-limiting adverse effects. Although only a small number of patients had been treated with lorazepam, the authors became sufficiently concerned with the adverse effects to terminate that arm of the protocol early. CONCLUSIONS: Symptoms of delirium in medically hospitalized AIDS patients may be treated efficaciously with few side effects by using low-dose neuroleptics (haloperidol or chlorpromazine). Lorazepam alone appears to be ineffective and associated with treatment-limiting adverse effects.

ABSTRACT RICHIESTA 2:

1. Murray-Braun

Nausea and vomiting common symptoms in patients with terminal, incurable illnesses. Both nausea and vomiting can be distressing. Haloperidol is commonly prescribed to relieve these symptoms. This is an updated version of the original Cochrane review published in Issue 2, 2009, of Haloperidol for the treatment nausea and vomiting in palliative care patients. To evaluate the efficacy and adverse events associated with the use of haloperidol for the treatment of nausea and vomiting in palliative care patients. We searched controlled trials registers in March 2015 to identify any ongoing or unpublished trials. We considered randomised controlled trials (RCTs) of haloperidol for the treatment of nausea or vomiting, or both, in any setting, for inclusion. The studies had to be conducted with adults receiving palliative care or suffering from an incurable progressive medical condition. We imported records from each of the electronic databases into a bibliographic package and merged them into a core database where we inspected titles, keywords and abstracts for relevance. If it was not possible to accept or reject an

abstract with certainty, we obtained the full text of the article for further evaluation. The two review authors independently assessed studies in accordance with the inclusion criteria. There were no differences in opinion between the authors with regard to the assessment of studies. We considered 27 studies from the 2007 search. In this update we considered a further 38 studies from the 2013 search, and two in the 2014 search. We identified one RCT of moderate quality with low risk of bias overall which met the inclusion criteria for this update, comparing ABH (Ativan®, Benadryl®, Haldol®) gel, applied to the wrist, with placebo for the relief of nauseain 22 participants. ABH gel includes haloperidol as well as diphenhydramine and lorazepam. The gel was not significantly better than placebo in this small study; however haloperidol is reported not to be absorbed significantly when applied topically, therefore the trial does not address the issue of whether haloperidol is effective or well□tolerated when administered by other routes (e.g. bymouth, subcutaneously or intravenously). We identified one ongoing trial of haloperidol for the management of nausea and vomitingin patients with cancer, with initial results published in a conference abstract suggesting that haloperidol is effective for 65% of patients. The trial had not been fully published at the time of our review. A further trial has opened, comparing oral haloperidol with oral methotrimeprazine (levomepromazine) for patients with cancer and nausea unrelated to their treatment, which we aim to include in the next review update. Since the last version of this review, we found one new study for inclusion but the conclusion remains unchanged.

There is incomplete evidence from published RCTs to determine the effectiveness of haloperidol for nausea andvomiting in palliative care. Other than the trial of ABH gel vs placebo, we did not identify any fully published RCTs exploring the effectiveness of haloperidol for nausea and vomiting in palliative care patients for this update, but two trials are underway.

2. Critchley P

Haloperidol is used commonly for the control of nausea and vomiting (N/V) in palliative care patients, but there is very little evidence to support its use. To assess the efficacy of haloperidol as an antiemetic in patients with cancer and N/V not related to cancer treatment. Patients with an N/V score of at least 1 on a 4-point scale were prescribed either oral or subcutaneous haloperidol. N/V and toxicity were assessed daily for the duration of the study (maximum five days) by both the patient and an observer (health professional). At Day 2, 33 of 42 (79%) treated patients were assessable for response. Eight (24%; 95% confidence interval [CI]: 10%–39%) patients had complete control of N/V and 12 (36%; 95% CI: 20%–53%) had partial control, giving an overall response rate of 61% (95% CI: 44%–77%). At Day 5, 23 patients were assessable for response. The overall response rate was 17 of 23 (74%; 95% CI: 56%–92%). If all patients are included in the response analysis, the overall response rates at Days 2 and 5 were 47% and 40%, respectively. Haloperidol has some efficacy in the treatment of N/V in this patient group. The results from this uncontrolled study provide pilot data from which to plan future controlled trials of antiemetics in the palliative care population.

3. Hardy JR.

Haloperidol is used commonly for the control of nausea and vomiting (N/V) in palliative care patients, but there is very little evidence to support its use. To assess the efficacy of haloperidol as an antiemetic in patients with cancer and N/V not related to cancer treatment. Patients with an N/V score of at least 1 on a 4-point scale were prescribed either oral or subcutaneous haloperidol. N/V and toxicity were assessed daily for the duration of the study (maximum five days) by both the patient and an observer (health professional). RESULTS: At Day 2, 33 of 42 (79%) treated patients were assessable for response. Eight (24%; 95% confidence interval [CI]: 10%-39%) patients had complete control of N/V and 12 (36%; 95% CI: 20%-53%) had partial control, giving an overall response rate of 61% (95% CI: 44%-77%). At Day 5, 23 patients were assessable for response. The overall response rate was 17 of 23 (74%; 95% CI: 56%-92%). If all patients are included in the response analysis, the overall response rates at Days 2 and 5 were 47% and 40%, respectively. CONCLUSION: Haloperidol has some efficacy in the treatment of N/V in this patient group. The results from this uncontrolled study provide pilot data from which to plan future controlled trials of antiemetics in the palliative care population.

4. Perkins P

BACKGROUND: Nausea and vomiting are common symptoms of patients with terminal, incurable illnesses and can be distressing. OBJECTIVES: The primary objective of the review was to evaluate the efficacy and adverse events associated with the use of haloperidol for the treatment of nausea and vomiting in palliative care patients. SEARCH STRATEGY: Several electronic databases were searched including CENTRAL, MEDLINE, EMBASE, CINAHL and AMED, using relevant search terms and synonyms. Handsearching complemented electronic searches (using reference lists of included studies, relevant chapters and review articles). There were no language restrictions imposed. Database searching was performed between 2nd and 16th September 2007. SELECTION CRITERIA: Studies considered for inclusion were randomised controlled trials (RCTs) of haloperidol for the treatment of nausea or vomiting, or both, in any setting. The studies had to be conducted with adults receiving palliative care or suffering from an incurable progressive medical condition. Studies where nausea or vomiting, or both, thought to be secondary to pregnancy or surgery were excluded. DATA COLLECTION AND ANALYSIS: Records from each of the electronic databases were imported into a bibliographic package and merged into a core database where titles, keywords and abstracts were inspected for relevance. If it was not possible to accept or reject an abstract with certainty, the full text of the article was obtained for further evaluation. The two review authors independently assessed studies in accordance with the inclusion criteria. There were no differences in opinion between authors with regard to assessment of studies. MAIN RESULTS: No RCTs were identified meeting the inclusion criteria. Twenty-six studies were considered but all were excluded from the review. AUTHORS' CONCLUSIONS: We did not identify any RCTs exploring the effectiveness of haloperidol for nausea and vomiting in palliative care patients.

5. Gordon P.

Nausea and vomiting are very common symptoms in cancer both treatment and non-treatment related. Many complications of advanced cancer such as gastroparesis, bowel and out let obstructions, and brain tumors may have nausea and vomiting or either symptom alone. In an on-obstructed situation, nausea may be more difficult to manage and ismoreobjectionableto patients.There is little research on management of these symptoms exceptthe literature on chemotherapy induced nausea where guidelines exist.This article will review the etiologies of nausea and vomiting in advanced cancer and the medications which have been used to treat them. An etiology based protocol to approach the symptom is outlined.

6. Gupta M.

Nausea and vomiting are common and distressing symptoms in advanced cancer. Both are multifactorial and cause significant morbidity, nutritional failure, and reduced quality of life. Assessment includes a detailed history, physical examination and investigations for reversible causes. Assessment and management will be influenced by performance status, prognosis, and goals of care. Several drug classes are effective with some having the added benefit of multiple routes of administration. It is our institution's practice to recommend metoclopramide as the first drug with haloperidol as an alternative antiemetic. Dexamethasone should be used for patients with central nervous system metastases or bowel obstruction. If your patient is near death, empiric metoclopramide, haloperidol or chlorpromazine is used without further investigation. For patients with a better prognosis, we exclude reversible causes and use the same first-line antiemetics, metoclopramide and haloperidol. For those who do not respond to first-line single antiemetics, olanzapine is second line and ondansetron is third. Rarely do we use combination therapy or cannabinoids. Olanzapine as a single agent has a distinct advantage over antiemetic combinations. It improves compliance, reduces drug interactions and has several routes of administration. Antiemetics, anticholinergics, octreotide and dexamethasone are used in combination to treat bowel obstruction. In opiod-naïve patients, we prefer haloperidol, glycopyrrolate and an opioid as the first-line treatment and add or substitute octreotide and dexamethasone in those who do not respond. Non-pharmacologic interventions (mechanical stents and percutaneous endoscopic gastrostomy tubes) are used when nausea is refractory to medical management or for home-going management to relieve symptoms, reduce drug costs and rehospitalization.

7. McLean SL

Nausea and vomiting are common symptoms in palliative care. Haloperidol is often used as an antiemetic in this context, although direct evidence supporting this practice is limited. To evaluate the efficacy and clinical use of haloperidol as an antiemetic in nonpalliative care contexts to inform practice, the authors conducted a rapid review of (i) published evidence to supplement existing systematic reviews, and (ii) practical aspects affecting the use of haloperidol including formulations and doses that are commonly available internationally. In nausea and vomiting related to cancer treatment, haloperidol was superior to control in two small studies. In postoperative nausea and vomiting (PONV), two

randomized controlled trials found treatment with haloperidol comparable to ondansetron. In palliative care, an observational study found a complete response rate of 24% with haloperidol (one in four patients) which would be consistent with a number needed to treat (NNT) of 3 to 5 derived from PONV. There remains insufficient direct evidence to definitively support the use of haloperidol for the management of nausea and vomiting in palliative care. However, generalizing evidence from other clinical contexts may have some validity.

8. Walsh

PURPOSE: The aim of this paper is to review the existing literature related to the management of nausea and vomiting (N & V) in advanced cancer and derive clinical evidence-based recommendations for its management. METHODS: Available systematic reviews on antiemetic drug effectiveness were used. One generic systematic review of antiemetics in advanced cancer (to 2009) was updated to February 2016. Agreement on recommendations was reached between panel members, and these were voted in favor unanimously by the larger antiemetic committee membership (n=37). RESULTS:The evidence base in this field is minimal with largely poor quality trials or uncontrolled trials and case studies. The level of evidence in most studies is low. The drug of choice for managing N & V in advanced cancer is metoclopramide titrated to effect. Alternative options include haloperidol, levomepromazine, or olanzapine. For bowel obstruction, the recommendation is to use octreotide given alongside an antiemetic (haloperidol) and where octreotide is not an option to use an anticholinergic antisecretory agent. For opioid-induced N & V, no recommendation could be made. CONCLUSION:These new guidelines, based on the existing (but poor) evidence, could help clinicians manage more effectively the complex and challenging symptoms of N & V in advanced cancer.

4.2. BUTILSCOPOLAMINA – IOSCINA BUTILBROMURO

USO *OFF-LABEL* CHE SI VUOLE AUTORIZZARE:

1. Somministrazione SC, anche in combinazione con altri farmaci, in infusione continua
2. Somministrazione SC/EV per riduzione delle secrezioni tracheobronchiali nel paziente in cure palliative in fase terminale di malattia (aspettativa di vita presumibile < 2 settimane)
3. Somministrazione SC/EV per la riduzione delle secrezioni gastrointestinali nell'ostruzione gastrointestinale non responsiva a trattamenti guaritivi chirurgici o farmacologici nel paziente in cure palliative con breve aspettativa di vita (presumibile < 3 mesi)

RAZIONALE DELLA RICHIESTA:

1. L'utilizzo di n-butilbromuro di joscina per **via sottocutanea** è comune in cure palliative, in particolare mediante un infusore, in cui vengono associati più farmaci con diversa indicazione di trattamento concomitante. Lo scopo di questa particolare attenzione è quello di contenere e ridurre la sofferenza al massimo possibile nella fase terminale della vita, per qualsiasi patologia, utilizzando le migliori tecniche e terapie mediche a disposizione, per permettere al malato una fine vita quanto più dignitosa e serena possibile.
2. Il fine vita è spesso accompagnato dal **rantolo terminale**. Si tratta di un rumore respiratorio, presente nel 30-90% dei pazienti con patologia oncologica in fase terminale di malattia, che deriva dal passaggio dell'aria attraverso secrezioni ristagnanti in faringe e trachea, che il paziente non è più in grado di espellere per diminuzione dello stato di coscienza, riduzione- abolizione del riflesso della tosse e della capacità di deglutire. La maggior parte dei dati in letteratura riporta un'incidenza variabile dal 31% al 92% del rantolo nelle ultime ore o giorni di vita. È un rumore talvolta udibile chiaramente anche al di fuori della stanza del malato e per questo è spesso causa di grave disagio per i familiari. Il trattamento può essere di tipo non farmacologico (variazione della postura) o farmacologico; la terapia farmacologica si basa sull'uso di farmaci con azione anticolinergica, che agiscono sui recettori muscarinici presenti nelle ghiandole salivari e nella mucosa delle vie aeree, con l'obiettivo di inibire la produzione di secrezioni tracheobronchiali.
3. **L'occlusione intestinale** è una complicanza che si rileva nei malati con patologie oncologiche che originano a livello addomino-pelvico o come manifestazione di metastasi; il quadro clinico si caratterizza per la presenza di nausea, vomito, dolore, alvo chiuso a feci e gas. La prevalenza nei malati di tumore è stimata dal 3% al 15% dei pazienti; la sopravvivenza mediana nei pazienti con occlusione gastrointestinale conclamata di 4-5 settimane. I tumori primitivi che danno più frequentemente origine a quadri di occlusione gastro-intestinale sono: colon 25-40%, ovaio 16-29%, stomaco 6-19%, pancreas 6-13%, vescica 3-10%, endometrio 3-11%. La diagnosi di tumore spesso coincide con la diagnosi di occlusione intestinale (13-32%). La gestione del quadro clinico può comprendere interventi di chirurgia o trattamenti endoscopici e terapia medica antiblastica, tuttavia, pazienti con malattia avanzata, o con condizioni generali compromesse e con breve aspettativa di vita (presumibile < 3 mesi) non sono

candidabili a terapie specifiche e richiedono una gestione unicamente dei sintomi causati dalla occlusione intestinale.

SITUAZIONE ATTUALE APPROVATA:

Manifestazioni spastico-dolorose del tratto gastroenterico e genito-urinario

Compresse rivestite: Pz>14 anni

Supposte: Pz>6 anni

Fiale per via intramuscolare o endovenosa ai soli pazienti adulti

RICERCA BIBLIOGRAFICA RICHIESTA 1:

Parole chiave: Hyoscine butylbromide, cancer, palliative care

Lavori evidenziati:

1. Barcia E, Reyes R, Azuara M.L, Sánchez Y, Negro S.:Compatibility of haloperidol and hyoscine-N-butyl bromide in mixtures for subcutaneous infusion to cancer patients in palliative care. Support Care Cancer 2003 ; 11, 2: 107-113.
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6. Agenzia Italiana del Farmaco, Guida all'uso dei farmaci, 233, 2008.

RCT DISPONIBILI:

No

RICERCA BIBLIOGRAFICA RICHIESTA 2:

Parole chiave: Hyoscine butylbromide, *death rattle*, cancer, palliative care

Lavori evidenziati:

1. Clark K[1], Currow DC, Agar M, Fazekas BS, Abernethy AP. *A pilot phase II randomized, cross-over, double-blinded, controlled efficacy study of octreotide versus hyoscine hydrobromide for control of noisy breathing at the end-of-life.* J Pain Palliat Care Pharmacother. 2008;22(2):131-8.
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4. Wildiers H et al. *Atropine, hyoscine butylbromide, or scopolamine are equally effective for the treatment of death rattle in terminal care*. J Pain Symptom Manage 39:124, 2009.
5. Mercadante S. et al. *Refractory death rattle: deep aspiration facilitates the effects of antisecretory agents*. J Pain Symptom Manage 41; 637, 2011.

RCT DISPONIBILI:

Sì, abstract 1-4

RICERCA BIBLIOGRAFICA RICHIESTA 3:

Parole chiave: *Hyoscine butylbromide, Malignant bowel obstruction, palliative care*

Lavori evidenziati:

1. Ripamonti C. et al.: *Role of octreotide, scopolamine butylbromide, and hydration in symptom control of patients with inoperable bowel obstruction and nasogastric tubes: a prospective randomized trial*. J Pain Symptom Manage 19:23–34, 2000.
2. Ripamonti CI. et al. *Management of malignant bowel obstruction*. Eur J Cancer; 44:1105, 2008.
3. Klein C, Stiel S, Bükki J, Ostgathe C**,** *Pharmacological treatment of malignant bowel obstruction in severely ill and dying patients: a systematic literature review*. Schmerz. Sep;26 (5):587-99, 2012.

RCT DISPONIBILI:

Sì, abstract 1

COMMENTI E CONCLUSIONI:

Impiego di **IOSCINA BUTILBROMURO SC/EV** per riduzione delle secrezioni tracheobronchiali nel paziente in cure pallaitive in fase terminale di malattia (aspettativa di vita presumibile < 2 settimane). La Letteratura, in 2 ultime revisioni, afferma che non vi sono studi prospettici di buona qualità randomizzati vs il placebo per dire che l'intervento farmacologico sia più efficace del placebo. Pertanto sembra non riconoscere la difficoltà di condurre tale tipologia di studi in pazienti in fase critica di malattia - per motivi etici relativi alla acquisizione del consenso informato- e che l'appropriato utilizzo è ampiamente dimostrato da numerose ricerche di confronto fra farmaci. Vi sono infatti studi che evidenziano una risposta, con attenuazione-risoluzione del rantolo, che arriva fino 54-71% dei casi trattati con antimuscarinici. In uno dei più importanti studi clinici, aperto, randomizzato, controllato di fase III, Wildiers H, ha confrontato gli effetti di scopolamina, atropina e butilbromuro di ioscina somministrati per via sottocutanea in bolo e successivamente in infusione continua in 333 pazienti terminali. L'efficacia dei farmaci è stata del 37- 42% dopo 1 ora dal suo utilizzo: per il N-Butilbromuro di Ioscina l'efficacia è stata dimostrata a dosaggi compresi tra 20-80 mg/die per via sottocutanea. La durata media dell'infusione fino al decesso è stata pari a 39,2 ore. Ai dosaggi utilizzati per ciascuno dei principi attivi non sono state rilevate differenze significative per efficacia e comparsa di effetti indesiderati e per tutti i farmaci studiati è risultato essere raccomandato un uso precoce, alla prime evidenze di comparsa del rantolo terminale.

Per tali riscontri, oltre alla considerazione che esistono indiscusse raccomandazioni di esperti, il N- Butilbromuro di Ioscina è stato inserito dal Western Australia nell'elenco dei farmaci utili al controllo del rantolo terminale e nel 2013 dal WHO nell'elenco dei farmaci essenziali in cure palliative (New Recommended Formulation). Testi specifici di cure palliative mostrano evidenze di efficacia e consuetudine nell'utilizzo nei pazienti in cure palliative al termine della vita che presentano rantolo.

Bibliografia aggiuntiva di commento alla nota:

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Impiego di **IOSCINA BUTILBROMURO** per la riduzione delle secrezioni gastrointestinali nell'ostruzione gastrointestinale non responsiva a trattamenti guaritivi chirurgici o farmacologici nel paziente paziente in cure palliative con breve aspettativa di vita (presumibile < 3 mesi).

N-butilbromuro di ioscina trova in cure palliative un importante e diffuso impiego, legato alla necessità di ridurre le secrezioni gastrointestinali e la sintomatologia dolorosa da spasmi viscerali in presenza di occlusione intestinale neoplastica inoperabile. La gestione farmacologica del quadro clinico prevede l'utilizzo di farmaci antiemetici ad azione centrale, analgesici, antisecretori. Il N- Butilbromuro di Ioscina potrebbe pertanto essere considerato fra le terapie farmacologiche di prima scelta o in aggiunta ad altri farmaci (utilizzati in modalità *off-label* quali l'octreotide), rispetto al trattamento endoscopico o chirurgico palliativo sia per l'azione antisecretoria che antispastica, nonché per il basso costo. La somministrazione consigliata, soprattutto nel *setting* domiciliare, è quella sottocutanea in infusione continua. Numerosi lavori di compatibilità fisica e chimica indicano che il butilbromuro di ioscina è compatibile in associazione con la maggior parte dei farmaci utilizzati in cure palliative. Testi specifici di cure palliative mostrano evidenze di efficacia e consuetudine nell'utilizzo nei pazienti in cure palliative al termine della vita che presentano occlusione intestinale non responsiva trattamenti guaritivi chirurgici o farmacologici.

Bibliografia aggiuntiva di commento alla nota:

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ABSTRACT RICHIESTA 1:

1. Barcia E.

The administration of drugs by s.c. infusion is routinely practiced in palliative medicine for the management of patients who are no longer able to take oral medication. It is not uncommon for two or more drugs to be combined in s.c. infusion solutions. Unfortunately,

the compatibility and stability of haloperidol and hyoscine- N-butyl bromide has not yet been determined. The objective of this study was to study the compatibility and stability of solutions containing both drugs in polypropylene syringes. Nine different solutions were assessed for up to 15 days following preparation. The solutions were prepared in polypropylene syringes with 0.9% saline as a diluent and stored at 4 degrees C and 25 degrees C. High-performance liquid chromatography was the analytical technique used to measure haloperidol and hyoscine- N-butyl bromide. The initial concentration ranges were 0.3125-1.25 mg/ml for haloperidol and 2.5-10.0 mg/ml for hyoscine- N-butyl bromide. Haloperidol was precipitated at a concentration of >/=1.25 mg/ml when it was combined with hyoscine- N-butyl bromide. Concentrations of hyoscine- N-butyl bromide lower than 10 mg/ml in mixtures with haloperidol or 0.625 mg/ml of haloperidol in mixtures with hyoscine- N-butyl bromide for s.c. infusion allow for the administration of both drugs without any significant loss after storage at 25 degrees C for periods of up to 15 days, with approximately >/=90% and 88%, respectively, of haloperidol and hyoscine- N-butyl bromide remaining. However, after storage of the mixtures for equivalent periods at 4 degrees C the losses of hyoscine- N-butyl bromide observed at the end of the study were higher than 20%, while the percentages of haloperidol remaining after 15 days at this temperature were >/=94.37%.

2. Barcia E.

The aim of this study was to determine the compatibility and stability of morphine hydrochloride and hyoscine-N-butyl bromide combined in solution at three different concentrations and stored in polypropylene syringes at 4 degrees C and 25 degrees C over a period of 15 days. The doses assayed were 20, 60 and 120 mg/day for morphine hydrochloride and 40, 60 and 80 mg/day for hyoscine-N-butyl bromide. These dose ranges were chosen according to daily practice. At both temperatures, all mixtures can be considered as physically compatible since no evidence of incompatibility-that is precipitation, turbidity, colour change or opacity and gas production-were observed. After 15 days of storage, the percentages of hyoscine-N-butyl bromide remaining in the drug mixtures tested ranged between 96.07% and 92.23%. At the end of the study, the percentages of morphine hydrochloride remaining in the drug mixtures were 100% at both temperatures.

3. Negro S.

The administration of drugs by subcutaneous infusion is routinely practiced in palliative medicine for the management of patients who are no longer able to take oral medication. It is common for two or more drugs to be combined in subcutaneous solutions. The combination of an opioid with other drugs (haloperiol lactate and hyoscine N-butyl bromide) can be very valuable. Unfortunately, the compatibility and stability of morphine hydrochloride, haloperidol lactate and hyoscine N-butyl bromide combined in the same solution has not yet been determined. Therefore, this study examined the stability of ternary solutions containing morphine HCl, haloperidol lactate and hyoscine N-butyl bromide at different dose ranges. Twelve different solutions were assessed for 15 days after preparation in polypropylene syringes using 0.9% saline as diluent. Triplicate syringes were stored at 25 degrees C. HPLC was the analytical technique used to

measure morphine HCl, haloperidol lactate and hyoscine N-butyl bromide. Initial concentration ranges were 1.67-10.0 mg/ml for morphine HCl, 0.417-0.625 mg/ml for haloperidol lactate and, 5.0-6.67 mg/ml for hyoscine N-butyl bromide. All three drugs were very stable (>92.5%) when stored at 25 degrees C. The clinical performance of the admixture was retrospectively assessed in 21 terminal oncology patients. Total symptom control was achieved in 17 out of 21 patients with very good local tolerance.

4. Barsia E.

More than two-thirds of patients with metastatic cancer experience pain. Tramadol is one of the most interesting and useful weak opioids used by palliative care units to treat moderate to moderately severe pain. Relief of distressful symptoms in terminally ill patients is of prime importance; a common practice is to administer opioid analgesics in conjunction with other drugs as hyoscine N-butyl bromide, which is very useful in reducing secretions in patients with inoperable malignant bowel obstruction. The pursuit for excellence in symptom control in patients unable to take oral medication has led to the administration of medications by other routes such as the subcutaneous route.

5. Negro S.

Combination of drugs for subcutaneous infusion is common practice in palliative medicine, however, there is no information pertaining to the compatibility and stability of tramadol combined in ternary admixtures and no information exists regarding its clinical performance. Tramadol hydrochloride, haloperidol lactate, and hyoscine N-butyl bromide have been examined for compatibility and stability when combined in solution under conditions mimicking their potential use via subcutaneous infusion in terminal oncology patients. Concentration ranges were 8.8-33.3 mg/mL, 0.208-0.624 mg/mL, and 3.33-6.67 mg/mL for tramadol hydrochloride, haloperidol lactate, and hyoscine N-butyl bromide. With these, 27 different admixtures were prepared and stored at 25 degrees C using 0.9% saline as diluent. Quantification was performed by high-performance liquid chromatography (HPLC). The clinical performance of the admixture was retrospectively assessed in 28 terminal oncology patients exhibiting Karnofsky's indexes of 10%-20%. All three drugs were very stable (>92%) at 25 degrees C for 15 days. Pain was completely controlled in all patients. Fifty percent of the patients suffered from 3-5 vomiting episodes per day and of these, 75% experienced complete control of the episodes. None of the patients showed local reactions after subcutaneous administration of the admixture. Our results confirm the compatibility and stability of the ternary admixture and its utility in highly vulnerable patients exhibiting moderate symptoms.

ABSTRACT RICHIESTA 2:

1. Clark K.

Noisy breathing at the end of life (noisy breathing ("NB") occurs in up to 90% of people. Interventions have not been systematically evaluated. There has been clinical observation

coupled with a proposed mechanism of effect that supports a role for octreotide in management of NB. The aim of this phase II study was to assess ten completed participants for the feasibility of an adequately powered phase III study. This randomized, double-blind, crossover pilot trial recruited participants from an inpatient palliative unit. Participants while well and their proxies simultaneously provided written informed consent. If NB were encountered, people were randomized to 200 mcg octreotide or 400 mcg hyoscine hydrobromide subcutaneously. If subsequent treatment was needed, the other medication was administered. A five point categorical scale documented the nurses' assessment of secretions over six hours. Eighty participants were consented of whom 10 (3 females, 7 males; median age 79, all with advanced cancer) received medication, five in each arm. There was no difference in the median time to administration of the second medication (3 hours). Two participants in each arm had a 2 category reduction of intensity after the second medication. Although feasible to consent and study this population in a way that respects autonomy and dignity even in the terminal hours of life, this pilot study suggests reconsideration of the pharmacological interventions (choice of agents, dosing, timing of dosing and pharmacokinetic profiles), standardizing of non-pharmacological care; and ways to measure directly family distress before further randomized studies for this symptom.

2. Likar R.

The aim of this randomized double-blind placebo-controlled study was to assess the efficacy of hyoscine hydrobromide in terminal cancer patients with cognitive impairment suffering from death rattle. The study was approved by the local ethics committee of the Klagenfurt General Hospital. The patients were randomized into 2 groups. Group A received hyoscine hydrobromide in a dose of 0.5 mg ad 1 ml NaCl intravenously (iv) or subcutaneously (sc). Group B received 1 ml of physiologic saline iv or sc. The patients received injections of substance A or B within the first 8 hours four-hourly, at time 0, 4 and 8 hours. From the 12^{th} hour on the study was performed openly with four-hourly applications of hyoscine hydrobromide 0.5 mg iv or sc. In addition, standardized sedatives were administered as required and the analgesic therapy continued either orally or, if necessary, sc or iv in equipotent doses. Every 2 hours death rattle was assessed and rated on a scale of 1 to 5 (1 = audible breathing noises, 5 = very severe rattling noises). In addition, restlessness and expressions of pain were assessed and rated on a scale of 1 to 3 (1 = mild, 2 = moderate, 3 = severe). RESULTS: Thirty-one patients were included in the study. Fifteen patients entered group A and 16 patients entered group B. There were no significant differences with respect to age, weight, diagnosis distribution or other demographic data. Group A demonstrated a tendency to less death rattle than group B in first 10 hours, however, this difference was not significant. Expressions of pain, however, were significantly greater in group A compared with group B, and there was a greater tendency to restlessness in group A compared to group B. CONCLUSION: Hyoscine hydrobromide given in a dose of 0.5 mg every four hours demonstrated only a minimal reduction of death rattle, and a greater incidence of expressions of pain and restlessness. Hyoscine hydrobromide in this dosage does not appear to be an effective therapeutic agent for type 1 of death rattle.

3. Likar R.

Death rattle is an extremely distressing symptom for the dying patient and for his environment. The aim of this study was to assess the efficacy of glycopyrronium bromide as compared with scopolamine hydrobromide in alleviating death rattle in terminal cancer patients with cognitive impairment. In a randomized, controlled study design patients were allocated in two groups. Group A received scopolamine hydrobromide in a dose of 0.5 mg intravenously every 6 hours for a period of 12 hours, group B received glycopyrronium bromide 0.4 mg every 6 hours for a period of 12 hours. In addition, standardized sedatives were administered as required and the analgesic therapy continued either orally or, if necessary, subcutaneously or intravenously in equipotent doses. Every 2 hours death rattle was assessed and rated on a scale of 1 to 5 (1 = audible breathing noises, 5 = very severe rattling noises). In addition, restlessness and expressions of pain were assessed and rated on a scale of 1 to 3 (1 = mild, 2 = moderate, 3 = severe). RESULTS: 13 patients were included in the study, 7 patients were allocated to group A and 6 patients to group B. There were no significant differences in demographic data, age, weight and diagnosis distribution between the two groups. Group B demonstrated a significant reduction of death rattle in the first 12 hours (p = 0.029) in comparison to group A. There were no significant differences concerning the side effects (restlessness, expressions of pain) in both groups. Glycopyrronium bromide given in a dose of 0,4 mg every six hours demonstrated a significant reduction of death rattle compared to scopolamine hydrobromide. Concerning side effects (restlessness, expressions of pain) there was no difference between both substances.

4. Wildiers H.

Death rattle is a frequent symptom (25%–50%) in the terminal stage of life, but there is neither standardized treatment nor prospective investigation performed on the effectiveness of anticholinergic drugs. The aim of the present study was to investigate the effectiveness of three different anticholinergic drugs in the treatment of death rattle in the terminal stage of life. Terminal patients who developed death rattle were randomly assigned 0.5 mg atropine, 20 mg hyoscine butylbromide, or 0.25 mg scopolamine. Each treatment was initiated with a subcutaneous bolus, which was followed by continuous administration of the same drug. The intensity of death rattle and side effects were prospectively scored at different time points. Three hundred and thirty-three eligible patients were randomized to atropine, hyoscine butylbromide, or scopolamine after informed consent from the patient or the appointed representative. For the three drugs, death rattle decreased to a nondisturbing intensity or disappeared after one hour in 42%, 42%, and 37% of cases, respectively (P=0.72). Further, effectiveness improved over time without significant differences among the treatment groups (effectiveness at 24 hours was 76%, 60%, and 68%, respectively). In an analysis on the three groups together, treatment was more effective when started at a lower initial rattle intensity; median survival after start of therapy was 23.9 hours. These data suggest that there are no significant differences in effectiveness or survival time among atropine, hyoscine butylbromide, and scopolamine in the treatment of death rattle.

5. Mercadante S.

Anticholinergic drugs, including atropine, hyoscine butylbromide, and scopolamine, have been shown to be equally effective in the treatment of death rattle. However, anticholinergic drugs may only be effective in reducing the production of further secretions, rather than eliminating the existing ones. A case is described in which a preventive procedure was undertaken to carefully eliminate secretions before starting anticholinergic drugs. Airway aspiration under light anesthesia removed secretions before starting anticholinergic drugs. Low doses of propofol were given intravenously to make a laryngoscopy feasible, allowing the complete aspiration of large amounts of tracheal secretions. No death rattle was perceived until death. Relatives were satisfied with the treatment and the peaceful death. Antisecretory agents may only prevent further accumulation of fluids along the airways and in the pharynx. The use of these drugs, supplemented by this aspiration procedure in carefully selected patients, may help eliminate death rattle in patients with advanced illness who are unable to cough or swallow. Explanation and reassurance to relieve fears and concerns regarding a procedure aimed to improve the quality of end-of-life care are of paramount importance, and active collaboration in decision making facilitates a timely intervention. This preliminary experience may help further research on the best treatment at the end of life.

ABSTRACT RICHIESTA 3:

1. Ripamonti C.

Bowel obstruction may be an inoperable complication in patients with end-stage cancer. Scopolamine butylbromide (SB) and octreotide (OCT) have been successfully used with the aim of reducing gastrointestinal (GI) secretions to avoid placement of a nasogastric tube (NGT); however, there have been no comparative studies concerning the efficacy of these drugs. Furthermore, there is little information about the role played by parenteral hydration in symptom control of these patients. In a prospective trial that involved all 17 inoperable bowel-obstructed patients presenting to our services with a decompressive NGT, patients were randomized to OCT 0.3 mg/day or SB 60 mg/day for 3 days through a continuous subcutaneous infusion. Clinical data, survival time, and the time interval from the first diagnosis of cancer to the onset of inoperable bowel obstruction were noted. The intensity of pain, nausea, dry mouth, thirst, dyspnea, feeling of abdominal distension, and drowsiness were assessed by means of a verbal scale before starting treatment with the drugs under study (T0) and then daily for 3 days (T1, T2, T3). Moreover, daily information was collected regarding the quantity of GI secretions through the NGT, the oral intake of fluids, the quantity of parenteral hydration, and the analgesic therapy used. The NGT could be removed in all 10 home care and in 3 hospitalized patients without changing the dosage of the drugs. OCT significantly reduced the amount of GI secretions at T2 ($P = 0.016$) and T3 ($P = 0.020$). Compared to the home care patients, the hospitalized patients received significantly more parenteral hydration ($P = 0.0005$) and drank more fluids ($P = 0.025$). There was no difference in the daily thirst and dry mouth intensity in relation to the amount of parenteral hydration or the treatment provided (OCT or SB). Independent of antisecretory treatment, the patients receiving less parenteral hydration presented significantly more nausea (T0 $P = 0.002$; T1 $P = 0.001$; T2 $P = 0.003$; T3 $P = 0.001$) and drowsiness at T3 ($P < 0.5$). Pain relief was obtained in all 17 patients and only two patients required an increase in morphine dose at T1. All patients with inoperable malignant bowel

obstruction should undergo treatment with antisecretory drugs so as to evaluate the possibility of removing the NGT. When a more rapid reduction in GI secretions is desired, OCT should be considered as the first choice drug. Parenteral hydration over 500 ml/day may reduce nausea and drowsiness.

2. Ripamonti C.

Malignant bowel obstruction (MBO) is a common and distressing outcome particularly in patients with bowel or gynaecological cancer. Radiological imaging, particularly with CT, is critical in determining the cause of obstruction and possible therapeutic interventions. Although surgery should be the primary treatment for selected patients with MBO, it should not be undertaken routinely in patients known to have poor prognostic criteria for surgical intervention such as intra-abdominal carcinomatosis, poor performance status and massive ascites. A number of treatment options are now available for patients unfit for surgery. Nasogastric drainage should generally only be a temporary measure. Self-expanding metallic stents are an option in malignant obstruction of the gastric outlet, proximal small bowel and colon. Medical measures such as analgesics according to the W.H.O. guidelines provide adequate pain relief. Vomiting may be controlled using anti-secretory drugs or/and anti-emetics. Somatostatin analogues (e.g. octreotide) reduce gastrointestinal secretions very rapidly and have a particularly important role in patients with high obstruction if hyoscine butylbromide fails. A collaborative approach by surgeons and the oncologist and/or palliative care physician as well as an honest discourse between physicians and patients can offer an individualised and appropriate symptom management plan.

3. Klein C.

Malignant bowel obstruction (MBO) occurs in 3-6% of patients suffering from advanced cancer. The incidence of MBO is highest in patients with gynaecological and colorectal malignancies. Typical symptoms include nausea, vomiting, abdominal pain and constipation. Initially, these symptoms may be isolated and sporadic, becoming more and more intense later on. The suggested treatment includes surgical, interventional and pharmacological strategies depending on the symptom pattern and the performance status of the patient. This study investigates the current evidence of pharmacological treatment for MBO during the last days of life. A systematic literature search of the electronic databases PubMed/Medline and Embase from 1966-2011 was conducted. All retrieved publications were screened for relevance with regard to content and methodology on the basis of title and abstract. The full text was obtained for all relevant articles and for those articles where classification was unsure. The systematic literature search identified 5,431 papers. After screening, 90 publications were analyzed in detail. A total of 69 publications were excluded due to content or methodology. Finally, 21 manuscripts were considered for review. Only a few studies used high quality methodology and they all had rather small sample sizes. In summary, they show weak positive signs of efficacy for the use of somatostatin analogues or anticholinergics in the pharmacological treatment of MBO. These results do not lead to a clear evidence base for the pharmacological treatment of MBO in the last days of life. As adverse events were infrequent and clinical studies suggest efficient symptom relief, the authors recommend the use of octreotide as

the first line medication. Butylscopolamine may be an alternative, where octreotide is not available. Higher costs for octreotide compared with butylscopolamine have to be considered. Available data do not allow assessing the effect of corticosteroids on symptoms caused by MBO when given during the last days of life.

4.3. DESAMETASONE

USO *OFF-LABEL* CHE SI VUOLE AUTORIZZARE:

1. Somministrazione orale/EV/SC per **nausea e vomito** in pazienti in fase avanzata di malattia
2. Somministrazione EV/SC per **occlusione intestinale** in pazienti in fase terminale
3. Somministrazione EV/SC per **dispnea** in pazienti in fase terminale
4. Somministrazione EV/SC per **compressione midollare** in pazienti oncologici in fase terminale
5. Somministrazione orale/EV/SC come adiuvante nella **terapia antalgica** in pazienti in fase avanzata di malattia
6. Somministrazione orale/EV/SC per **astenia e sindrome anoressia-cachessia** in pazienti in fase avanzata di malattia

RAZIONALE DELLA RICHIESTA

1. **Nausea e vomito** sono sintomi comuni nei pazienti in fase avanzata di malattia e hanno un pesante impatto sulla qualità della vita, influiscono sulla possibilità di alimentarsi e sulla qualità del sonno. Il desametasone ha una importante attività antiemetica e viene utilizzato in aggiunta ad altri farmaci per il trattamento di nausea e vomito. I dosaggi proposti in letteratura sono compresi tra i 4 e gli 8 mg/die.
2. Nel caso dell'**occlusione intestinale**, i pazienti presentano sintomi particolarmente invalidanti quali dolore addominale, anoressia oltre a nausea e vomito ricorrente. Il desametasone rappresenta, normalmente in associazione con altre molecole quali metoclopramide ed aloperidolo, un farmaco di prima scelta per il controllo dei sintomi gastrointestinali con dosaggi compresi tra i 4 e gli 8 mg/die.
3. Nei pazienti con malattia in fase terminale la **dispnea** rappresenta un sintomo ricorrente, invalidante e con forte impatto sulla qualità della vita. Per il trattamento della dispnea, particolarmente in situazioni quali polmonite attinica o linfangite carcinomatosa, il desametasone rappresenta il trattamento di prima scelta con dosaggi normalmente compresi tra gli 8 mg/die ed i 24 mg/die.
4. In situazioni di **emergenza ricorrenti** nel *setting* delle cure palliative come la compressione midollare il desametasone rappresenta un farmaco capace di attenuare la sintomatologia correlata. In questi casi i dosaggi proposti oscillano tra 8 mg/die e 24 mg/die.
5. Nel **dolore da metastasi ossee** o in quello legato alla presenza di lesioni primitive o secondarie del fegato con tensione della capsula epatica il desametasone rappresenta un importante farmaco adiuvante nella terapia antalgica. I dosaggi proposti in letteratura sono compresi in questo caso tra i 4 e gli 8 mg/die.
6. **Astenia e sindrome anoressia-cachessia** sono condizioni che coinvolgono la maggior parte dei pazienti soprattutto nella fase terminale. Uno dei maggiori problemi per i pazienti che affrontano la fase terminale della vita ed hanno un pesante impatto sulla capacità di svolgere le normali attività della vita quotidiana e secondariamente sulla qualità della vita. Anche in questi casi il desametasone rappresenta una delle

armi disponibili per contrastare sintomi per i quali non sono disponibili altre alternative terapeutiche di tipo farmacologico. Secondo quanto riportato in letteratura i trattamenti dovrebbero essere di breve durata (non oltre le quattro settimane), utilizzando il dosaggio più basso possibile (da 2 a 4 mg/die) e dovrebbero essere sospesi scalando gradualmente le dosi soprattutto se il paziente non ottiene i benefici attesi. La via di somministrazione privilegiata in cure palliative, poiché risulta essere la meno invasiva, è quella sottocutanea e in letteratura è ampio il consenso sulla possibilità di utilizzare tale via senza rischi per il paziente in tutte le situazioni descritte.

Situazione attuale approvata:

- compresse e gocce per somministrazione orale: corticoterapia antinfiammatoria ed antiallergica, artrosi degenerativa e post-traumatica, poliartrite cronica evolutiva, spondiloartrite anchilosante, stati asmatici, dermatiti e dermatosi allergiche
- soluzione iniettabile per uso endovenoso o intramuscolare: 4 mg/1 ml per corticoterapia antinfiammatoria, artrosi degenerativa e post-traumatica, artrite infiammatoria, poliartrite cronica evolutiva, spondiloartrite anchilosante, accessi asmatici. 8 mg/2 ml per edema cerebrale, neoplasie cerebrali (come coadiuvante), stati di emergenza e shock vari: edema della glottide, reazioni post-trasfusionali, anafilassi, traumatismi emorragici, chirurgici, settici, cardiogeni, da ustioni.

RICERCA BIBLIOGRAFICA RICHIESTA 1:

Parole chiave: dexamethasone, nausea, vomiting

Lavori evidenziati:

1. Gupta M, DavisM, LeGrand S, Walsh D, Lagman R. Nausea and Vomiting in Advanced Cancer- “The Cleveland Clinic Protocol”. Journal Supportive Oncology, 2013 Mar;11(1):8-13
2. Vayne-Bossert P, Haywood A, Good P, Khan S, Rickett K, Hardy JR. Corticosteroids for adult patients with advanced cancer who have nausea and vomiting (not related to chemotherapy, radiotherapy, or surgery). Cochrane Database Syst Rev. 2017 Jul 3;7: CD012002.
3. Davis MP, Hallerberg G; Palliative Medicine Study Group of the Multinational Association of Supportive Care in Cancer. A systematic review of the treatment of nausea and/or vomiting in cancer unrelated to chemotherapy or radiation. J Pain Symptom Manage. 2010;39(4):756-767

RICERCA BIBLIOGRAFICA RICHIESTA 2:

Parole chiave: dexamethasone, bowel obstruction

Lavori evidenziati:

1. Berger J, Lester P, Rodrigues L. Medical Therapy of Malignant Bowel Obstruction with Octreotide, Dexamethasone and Metoclopramide. Am J Hosp Palliat Care. 2016 May;

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RICERCA BIBLIOGRAFICA RICHIESTA 3:

Parole chiave: dexamethasone, dyspnea, breathlessness

Lavori evidenziati:

1. Hui D, Kilgore K, Frisbee-Hume S, Park M, Tsao A, Delgado Guay M, Lu C, William W Jr, Pisters K, Eapen G, Fossella F, Amin S, Bruera E.J Dexamethasone for Dyspnea in Cancer Patients: A Pilot Double-Blind, Randomized, Controlled Trial. Pain Symptom Manage. 2016 Jul;52(1):8-16

RICERCA BIBLIOGRAFICA RICHIESTA 4:

Parole chiave: dexamethasone, spinal cord compression

Lavori evidenziati:

1. Skeoch GD, Tobin MK, Khan S, Linninger AA, Mehta AI. Corticosteroid Treatment for Metastatic Spinal Cord Compression: A Review. Global Spine J. 2017 May;7(3):272-279
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3. Sodji Q, Kaminski J, Willey C, Kim N, Mourad W, Vender J, Dasher B. Management of Metastatic Spinal Cord Compression. South Med J. 2017 Sep;110(9):586-593

RICERCA BIBLIOGRAFICA RICHIESTA 5:

Parole chiave: dexamethasone, pain treatment

Lavori evidenziati:

1. Leppert W, Buss T.The role of corticosteroids in the treatment of pain in cancer patients. Curr Pain Headache Rep. 2012 Aug;16(4):307-13
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3. Mishra S, Bhatnagar S, Gupta D, Nirwani Goyal G, Jain R, Chauhan H. Management of neuropathic cancer pain following WHO analgesic ladder: a prospective study. Am J Hosp Palliat Care. 2008 Dec-2009 Jan;25(6):447-51

RICERCA BIBLIOGRAFICA RICHIESTA 6:

Parole chiave: dexamethasone, fatigue, anorexia

Lavori evidenziati:

1. Yennurajalingam S, Williams JL, Chisholm G, Bruera E. Effects of Dexamethasone and Placebo on Symptom Clusters in Advanced Cancer Patients: A Preliminary Report. Oncologist. 2016 Mar;21(3):384-90
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ABSTRACT RICHIESTA 1:

1. Gupta M.

Nausea and vomiting are common and distressing symptoms in advanced cancer. Both are multifactorial and cause significant morbidity, nutritional failure, and reduced quality of life. Assessment includes a detailed history, physical examination and investigations for reversible causes. Assessment and management will be influenced by performance status, prognosis, and goals of care. Several drug classes are effective with some having the added benefit of multiple routes of administration. It is our institution's practice to recommend metoclopramide as the first drug with haloperidol as an alternative antiemetic. Dexamethasone should be used for patients with central nervous system metastases or bowel obstruction. If your patient is near death, empiric metoclopramide, haloperidol or chlorpromazine is used without further investigation. For patients with a better prognosis, we exclude reversible causes and use the same first-line antiemetics, metoclopramide and haloperidol. For those who do not respond to first-line single antiemetics, olanzapine is second line and ondansetron is third. Rarely do we use combination therapy or cannabinoids. Olanzapine as a single agent has a distinct advantage over antiemetic combinations. It improves compliance, reduces drug interactions and has several routes of administration. Antiemetics, anticholinergics, octreotide and dexamethasone are used in combination to treat bowel obstruction. In opiod-na'ive patients, we prefer haloperidol, glycopyrrolate and an opioid as the first-line treatment and add or substitute octreotide and dexamethasone in those who do not respond. Non-pharmacologic interventions (mechanical stents and percutaneous endoscopic gastrostomy tubes) are used when nausea is refractory to medical management or for home-going management to relieve symptoms, reduce drug costs and rehospitalization.

2. Vayne-Bossert P.

BACKGROUND: Nausea is a common symptom in advanced cancer, with a prevalence of up to 70%. While nausea and vomiting can be related to cancer treatments, such as chemotherapy, radiotherapy, or surgery, a significant number of people with advanced cancer also suffer from nausea unrelated to such therapies. Nausea and vomiting may also cause psychological distress, and have a negative impact on the quality of life of cancer patients; similarly to pain, nausea is often under-treated. The exact mechanism of action of corticosteroids on nausea is unclear, however, they are used to manage a number of cancer-specific complications, including spinal cord compression, raised intracranial pressure, and lymphangitis carcinomatosis. They are also commonly used in palliative care for a wide variety of non-specific indications, such as pain, nausea, anorexia, fatigue, and low mood. However, there is little objective evidence of their efficacy in symptom control, and corticosteroids have a wide range of adverse effects that are dose and time dependent. In view of their widespread use, it is important to seek evidence of their effects on nausea and vomiting not related to cancer treatment. OBJECTIVES: To assess the effects of corticosteroids on nausea and vomiting not related to chemotherapy, radiotherapy, or surgery in adult cancer patients. SEARCH METHODS: We searched CENTRAL, MEDLINE Ovid, Embase Ovid, CINAHL EBSCO, Science Citation Index Web of Science, Latin America and Caribbean Health Sciences (LILACS), Conference Proceedings Citation Index - Science Web of Science, and clinical trial registries, from inception to 23rd August 2016. SELECTION CRITERIA:Any double-blind randomised or prospective controlled trial that included adults aged 18 years and over with advanced cancer with nausea and vomiting not related to chemotherapy, radiotherapy, or surgery were eligible for the review, when using corticosteroids as antiemetic treatment. DATA COLLECTION AND ANALYSIS:All review authors independently assessed trial quality and extracted data. We used arithmetic means and standard deviations for each outcome to report the mean difference (MD) with 95% confidence interval (CI). We assessed the quality of the evidence using GRADE and created a 'Summary of findings' table. MAIN RESULTS: Three studies met the inclusion criteria, enrolling 451 participants. The trial size varied from 51 to 280 participants. Two studies compared dexamethasone to placebo, and the third study compared a number of additional interventions in various combinations, including metoclopramide, chlorpromazine, tropisetron, and dexamethasone. The duration of the studies ranged from seven to 14 days. We included two studies (127 participants) with data at eight days in the meta-analysis for nausea intensity; no data were available that incorporated the same outcome measures for the third study. Corticosteroid therapy with dexamethasone resulted in less nausea (measured on a scale of 0 to 10, with a lower score indicating less nausea) compared to placebo at eight days (MD 0.48 lower nausea, 95% CI 1.53 lower to 0.57 higher; very low-quality evidence), although this result was not statistically significant (P = 0.37). Frequency of adverse events was not significantly different between groups, and the interventions were well tolerated. Factors limiting statistical analysis included the lack of standardised measurements of nausea, and the use of different agents, dosages, and comparisons. Subgroup analysis according to type of cancer was not possible due to insufficient data. The quality of this evidence was downgraded by three levels, from high to very low due to imprecision, likely selection bias, attrition bias, and the small number of participants in the included studies. AUTHORS' CONCLUSIONS:There are few studies assessing the effects of corticosteroids on nausea and vomiting not related to chemotherapy, radiotherapy, or surgery in adult cancer patients. This review found very low-quality evidence which neither supported nor refuted corticosteroid use in this setting. Further high quality studies are needed to determine if corticosteroids are efficacious in this setting.

3. Davis MP, Hallerberg G.

CONTEXT: A systematic review of antiemetics for emesis in cancer unrelated to chemotherapy and radiation is an important step in establishing treatment recommendations and guiding future research. Therefore, a systematic review based on the question "What is the evidence that supports antiemetic choices in advanced cancer?" guided this review. OBJECTIVES:To determine the level of evidence for antiemtrics in the management of nausea and vomiting in advanced cancer unrelated to chemotherapy and radiation, and to discover gaps in the evidence, which would provide important areas for future research. METHODS: Three databases and independent searches using different MeSH terms were performed. Related links were searched and hand searches of related articles were made. Eligible studies included randomized controlled trials (RCTs), prospective single-drug studies, studies that used guidelines based on the etiology of emesis, cohort studies, retrospective studies, and case series or single-patient reports. Studies that involved treatment of chemotherapy, radiation, or postoperation-related emesis were excluded. Studies that involved the treatment of emesis related to bowel obstruction were included. The strength of evidence was graded as follows: 1) RCTs, A; 2) single-drug prospective studies, B1; 3) studies based on multiple drug choices for etiology of emesis, B2; and 4) cohort, case series, retrospective, and single-patient reports, E. Level of evidence was determined by the Oxford Centre for Evidence-Based Medicine Levels of Evidence (May 2001) (A, B, C, D). RESULTS:Ninety-three articles were found. Fourteen were RCTs, most of them of low quality, based either on lack of blinding, lack of description of the method of randomization, concealment, and/or attrition. Metoclopramide had modest evidence (B) based on RCTs and prospective cohort studies. Octreotide, dexamethasone, and hyoscine butylbromide are effective in reducing symptoms of bowel obstruction, based on prospective studies and/or one RCT. There was no evidence that either multiple antiemetics or antiemetic choices based on the etiology of emesis were any better than a single antiemetic. There is poor evidence for dose response, intraclass or interclass drug switch, or antiemetic combinations in those individuals failing to respond to the initial antiemetic. CONCLUSION:There are discrepancies between antiemetic studies and published antiemetic guidelines, which are largely based on expert opinion. Antiemetic recommendations have moderate to weak evidence at best. Prospective randomized trials of single antiemetics are needed to properly establish evidence-based guidelines.

ABSTRACT RICHIESTA 2:

1. Berger J.

BACKGROUND: Malignant bowel obstruction is a highly symptomatic, often recurrent, and sometimes refractory condition in patients with intra-abdominal tumor burden. Gastro-intestinal symptoms and function may improve with anti-inflammatory, anti-secretory, and prokinetic/anti-nausea combination medical therapy. OBJECTIVE: To describe the effect of octreotide, metoclopramide, and dexamethasone in combination on symptom burden and bowelfunction in patients with malignant bowel obstruction and dysfunction. DESIGN: A retrospective case series of patients with malignant bowel obstruction (MBO) and malignant bowel dysfunction (MBD) treated by a palliative care consultation service with octreotide, metoclopramide, and dexamethasone. Outcomes measures were nausea, pain, and time to resumption of oral intake. RESULTS: 12 cases with MBO, 11 had moderate/severe nausea on presentation. 100% of these had improvement in nausea by

treatment day #1. 100% of patients with moderate/severe pain improved to tolerable level by treatment day #1. The median time to resumption of oral intake was 2 days (range 1-6 days) in the 8 cases with evaluable data. Of 7 cases with MBD, 6 had For patients with malignant boweldysfunction, of those with moderate/severe nausea. 5 of 6 had subjective improvement by day#1. Moderate/severe pain improved to tolerable levels in 5/6 by day #1. Of the 4 cases with evaluable data on resumption of PO intake, time to resume PO ranged from 1-4 days. CONCLUSION: Combination medical therapy may provide rapid improvement in symptoms associated with malignant bowel obstruction and dysfunction.

2. Feuer DJ.

BACKGROUND:Gastrointestinal and ovarian cancers are common cancers. The incidence of associated malignant bowel obstruction in patients with advanced cancers of these types is not known, and the best management of these patients is controversial. Inappropriate management may result in uncontrolled (faeculant) vomiting, pain and distress. Management of the symptoms can include palliative surgery, nasogastric tube suction together with intravenous fluids, or pharmacological means, such as corticosteroids. There is uncertainty regarding both the efficacy and possible harmful effects of corticosteroids, and also the most effective type, dose/dosing regime, route and period of administration. OBJECTIVES:To locate, appraise and summarise evidence from scientific studies on intestinal obstruction due to advanced gynaecological and gastrointestinal cancer, in order to assess the efficacy of corticosteroids SEARCH STRATEGY: A comprehensive list of all studies was provided by an extensive search of the electronic databases, relevant journals, reference lists, the grey literature, contact with investigators and other search strategies outlined in the methods. SELECTION CRITERIA: As the review concentrates on the 'best evidencÈ available of the role of corticosteroids in malignant bowel obstruction due to advanced gynaecological and gastrointestinal cancer the inclusion criteria were kept fairly broad so as to include all studies relevant to the question DATA COLLECTION AND ANALYSIS:Data extraction forms were used to collect data from the studies included in the review. The data was checked by a secondary searcher to reduce error. A qualitative analysis was performed of the dichotomous data of resolution of obstructionand death at one month, obtained from the randomised controlled trials of corticosteroids versus placebo. Both fixed and random effect models were used. Number needed to treat (NNT) was derived from the odds ratio. Kaplan-Meier survival curves from individual patient data were also analysed. Studies of lower methodological quality were assessed in a qualitative manner. MAIN RESULTS:Three unpublished, randomised, placebo, double blind controlled trials and seven published (prospective and retrospective) trials were considered eligible. Using only the randomised trials, there is a trend, which is not statistically significant, for the resolution of bowel obstruction using corticosteroids. There is no statistically significant difference in mortality at one month, nor in the Kaplan-Meier curves, which describe the survival of patients on corticosteroids or placebo. Number needed to treat is 6 (3, infinity) ie six patients need to be treated with corticosteroids to resolve one episode of bowel obstruction. The results are robust to fixed and random effects models and to 'best' and 'worst casÈ scenarios on the missing data from patients. The morbidity associated with corticosteroids appears to be very low, though the quality of the data limits this conclusion. No other outcomes were available from the published data or from the authors. REVIEWER'S CONCLUSIONS:There is a trend for evidence that corticosteroids of dose range 6-16 mg dexamethasone given intravenously may bring about the resolution of bowel obstruction. Equally, the incidence

of side effects in all the included studies is extremely low. Corticosteroids do not seem to affect the length of survival of these patients.

ABSTRACT RICHIESTA 3:

1. Hui D.

CONTEXT: **Dexamethasone** is often used to treat dyspnea in cancer patients, but evidence is lacking. OBJECTIVES: We determined the feasibility of conducting a randomized trial of **dexamethasone** in cancer patients and estimated the efficacy of **dexamethasone** in the treatment of dyspnea. METHODS: In this double-blind, randomized, controlled trial, patients with dyspnea ≥4 were randomized to receive either **dexamethasone** 8 mg twice daily × four days then 4 mg twice daily × three days or placebo for seven days, followed by an open-label phase for seven days. We documented the changes in dyspnea (0-10 numeric rating scale), spirometry measures, quality of life, and toxicities. RESULTS:A total of 41 patients were randomized and 35 (85%) completed the blinded phase. **Dexamethasone** was associated with a significant reduction in dyspnea numeric rating scale of -1.9 (95% CI -3.3 to -0.5, P = 0.01) by Day 4 and -1.8 (95% CI -3.2 to -0.3, P = 0.02) by Day 7. In contrast, placebo was associated with a reduction of -0.7 (95% CI -2.1 to 0.6, P = 0.38) by Day 4 and -1.3 (95% CI -2.4 to -0.2, P = 0.03) by Day 7. The between-arm difference was not statistically significant. Drowsiness improved with **dexamethasone**. **Dexamethasone** was well tolerated with no significant toxicities. CONCLUSION: A double-blind, randomized, controlled trial of **dexamethasone** was feasible with a low attrition rate. Our preliminary data suggest that **dexamethasone** may be associated with rapid improvement in dyspnea and was well tolerated. Further studies are needed to confirm our findings.

ABSTRACT RICHIESTA 4:

1. Skeoch GD.

STUDY DESIGN: Narrative review. OBJECTIVE: Metastatic spinal cord compression (MSCC) is a very frequent complication among cancer patients. Presenting commonly as nocturnal back pain, MSCC typically progresses to lower extremity paresis, loss of ambulatory capabilities, and paraplegia. In addition to standard treatment modalities, corticosteroid administration has been utilized in preclinical and clinical settings as adjunctive therapy to reduce local spinal cord edema and improve clinical symptoms. This article serves as a review of existing literature regarding corticosteroid management of MSCC and seeks to provide potential avenues of research on the topic.

METHODS: A literature search was performed using PubMed in order to consolidate existing information regarding dexamethasone treatment of MSCC. Of all search results, 7 articles are reviewed, establishing the current understanding of metastatic spine disease and dexamethasone treatment in both animal models and in clinical trials. RESULTS: Treatment with high-dose corticosteroids is associated with an increased rate of potentially serious systemic side effects. For this reason, definitive guidelines for the use of dexamethasone in the management of MSCC are unavailable. CONCLUSIONS: It is

still unclear what role dexamethasone plays in the treatment of MSCC. It is evident that new, more localizable therapies may provide more acceptable treatment strategies using corticosteroids. Looking forward, the potential for more targeted, localized application of the steroid through the use of nanotechnology would decrease the incidence of adverse effects while maintaining the drug's efficacy.

2. Kumar A.

STUDY DESIGN: Systematic review. OBJECTIVES:We conducted a systematic review of the literature to answer the following questions regarding the use of steroid therapy in metastatic spinal cord compression (MSCC): 1. In cases of MSCC, what is the effect of steroid administration before definitive radiotherapy or surgery on ambulatory status, bowel and bladder function and survival? 2. What steroid dosing regimens are associated with the best outcomes concerning neurological symptoms and complication prevention in cases of MSCC? SUMMARY OF BACKGROUND DATA: Currently, there is significant variation in the initial bolus dose, daily maintenance dose and duration of treatment when steroids are used as a bridge to definitive therapy for MSCC. METHODS: A literature search following PRISMA guidelines was conducted in June 2016, using Medline via Ovid SP, Medline via PubMed, Embase, Biosis Previews and the Cochrane Library. Search terms used in each database varied slightly to optimize results. All generic steroid formulations were included along with spinal cord compression or myelopathy combined with metastatic or malignant tumors. Papers discussing acute traumatic causes of spinal cord compression were excluded, as were papers discussing cord compression from nonmetastatic tumors or epidural lipomatosis. Subjects were limited to adult humans undergoing definitive treatment with radiotherapy or surgery. RESULTS:Of the 309 papers retrieved, 66 full text studies were reviewed and 6 papers were found to address the stated questions. CONCLUSIONS: There is a paucity of high quality literature evaluating the use of steroids in MSCC. On the basis of the evidence available an initial 10 mg intravenous bolus of dexamethasone followed by 16 mg PO QD has been associated with fewer complications compared with 100 mg bolus and 96 mg QD. Weaning of steroids should occur rapidly after definitive treatment. Risk of gastric bleeding or perforation can be managed with the routine use of proton-pump inhibitors. LEVEL OF EVIDENCE: Level IIIa.

3. Sodji Q.

Cancer metastasis is a key event in tumor progression associated not only with mortality but also significant morbidity. Metastatic disease can promote end-organ dysfunction and even failure through mass effect compression of various vital organs including the spinal cord. In such cases, prompt medical attention is needed to restore neurological function, relieve pain, and prevent permanent damage. The three therapeutic approaches to managing metastatic spinal cord compression include corticosteroids, surgery, and radiation therapy. Although each may improve patients' symptoms, their combination has yielded the best outcome. In cancer patients with clinical suspicion of spinal cord compression, dexamethasone should be initiated followed by surgical decompression, when possible, and radiation. The latter becomes the preferred treatment in patients with inoperable disease.

ABSTRAT RICHIESTA 5:

1. Leppert W.

Pain is one of the most frequent and most distressing symptoms in the course of cancer. The management of pain in cancer patients is based on the concept of the World Health Organization (WHO) analgesic ladder and was recently updated with the EAPC (European Association for Palliative Care) recommendations. Cancer pain may be relieved effectively with opioids administered alone or in combination with adjuvant analgesics. Corticosteroids are commonly used adjuvant analgesics and play an important role in neuropathic and bone pain treatment. However, in spite of the common use of corticosteroids, there is limited scientific evidence demonstrating their efficacy in cancer patients with pain. The use of corticosteroids in spinal cord compression, superior vena cava obstruction, raised intracranial pressure, and bowel obstruction is better established than in other nonspecific indications. This review aims to present the role of steroids in pain and management of other symptoms in cancer patients according to the available data, and discusses practical aspects of steroid use.

2. Mercadante S.

This randomized controlled study evaluated the role of corticosteroids as adjuvants to opioid therapy in 76 advanced cancer patients with pain who requiring strong opioids. Patients were divided in 2 groups. Group O received conventional opioid treatment. Group OS received dexamethasone (8 mg orally) along with conventional treatment. Pain and symptom intensity, sense of well-being, and opioid escalation index and distress score were recorded at weekly intervals until death. No differences in pain intensity, opioid consumption, and opioid escalation index were found in 66 patients who survived 33 to 37 days. Corticosteroids did not provide significant additional analgesia to opioids, but persistently decreased opioid-related gastrointestinal symptoms for the patients with limited survival and improved the sense of well-being for some weeks. Corticosteroid-related toxicity was minimal. Further studies with an increased sample size are necessary to detect any minimal difference in analgesia between the two groups.

3. Mishra S.

Cancer pain treatment according to the guidelines of World Health Organization (WHO) is effective and safe in majority of patients. 818 neuropathic cancer pain patients were enrolled in the study and pain was managed according to WHO analgesic ladder and followed up to six months. Main adjuvant drugs used were amitryptaline (29.9%), gabapentin (29.9%) and gabapentine with dexamethasone in (19.9%) and dexamethasone alone in (20.2%) patients. Opioids prescribed were mainly tramadol, codeine sulphate and morphine. 52% patients received morphine as rescue analgesic. At the end of six months 53.2% patients had no pain and 41.9% of patients had mild pain as compared to 0% and 10.2% patients respectively at the first visit. 4.9% of patients had moderate pain even after the treatment. Neuropathic cancer pain can be relieved by multimodal treatment following WHO guidelines as majority of cancer patients suffered multiple types of pain.

ABSTRACT RICHIESTA 6:

1. Yennurajalingam

OBJECTIVE: Advanced cancer patients frequently experience debilitating symptoms that occur in clusters, but few pharmacological studies have targeted symptom clusters. Our objective was to examine the effects of dexamethasone on symptom clusters in patients with advanced cancer. METHODS: We reviewed the data from a previous randomized clinical trial to determine the effects of dexamethasone on cancer symptoms. Symptom clusters were identified according to baseline symptoms by using principal component analysis. Correlations and change in the severity of symptom clusters were analyzed after study treatment. RESULTS:A total of 114 participants were included in this study. Three clusters were identified: fatigue/anorexia-cachexia/depression (FAD), sleep/anxiety/drowsiness (SAD), and pain/dyspnea (PD). Changes in severity of FAD and PD significantly correlated over time (at baseline, day 8, and day 15). The FAD cluster was associated with significant improvement in severity at day 8 and day 15, whereas no significant change was observed with the SAD cluster or PD cluster after dexamethasone treatment. CONCLUSION: The results of this preliminary study suggest significant correlation over time and improvement in the FAD cluster at day 8 and day 15 after treatment with dexamethasone. These findings suggest that fatigue, anorexia-cachexia, and depression may share a common pathophysiologic basis. Further studies are needed to investigate this cluster and target anti-inflammatory therapies.

2. Mücke M.

BACKGROUND: This review updates the original review, 'Pharmacological treatments for fatigue associated with palliative care and also incorporates the review 'Drug therapy for the management of cancer-related fatigue. In healthy individuals, fatigue is a protective response to physical or mental stress, often relieved by rest. By contrast, in palliative care patients' fatigue can be severely debilitating and is often not counteracted with rest, thereby impacting daily activity and quality of life. Fatigue frequently occurs in patients with advanced disease (e.g. cancer-related fatigue) and modalities used to treat cancer can often contribute. Further complicating issues are the multidimensionality, subjective nature and lack of a consensus definition of fatigue. The pathophysiology is not fully understood and evidence-based treatment approaches are needed. OBJECTIVES: To evaluate the efficacy of pharmacological treatments for fatigue in palliative care, with a focus on patients at an advanced stage of disease, including patients with cancer and other chronic diseases. SEARCH METHODS: For this update, we searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, PsycINFO and EMBASE, and a selection of cancer journals up to 28 April 2014. We searched the references of identified articles and contacted authors to obtain unreported data. To validate the search strategy we selected sentinel references. SELECTION CRITERIA:We considered randomised controlled trials (RCTs) concerning adult palliative care with a focus on pharmacologicaltreatment of fatigue compared to placebo, application of two drugs, usual care or a non-pharmacological intervention. The primary outcome had to be non-specific fatigue (or related terms such as asthenia). We did not include studies on fatigue related to antineoplastic treatment (e.g. chemotherapy, radiotherapy, surgical intervention). We also included secondary outcomes that were assessed in fatigue-related studies (e.g.

exhaustion, tiredness). DATA COLLECTION AND ANALYSIS: Two review authors (MM and MC) independently assessed trial quality and extracted data. We screened the search results and included studies if they met the selection criteria. If we identified two or more studies that investigated a specific drug with the same dose in a population with the same disease and using the same assessment instrument or scale, we conducted meta-analysis. In addition, we compared the type of drug investigated in specific populations, as well as the frequent adverse effects of fatigue treatment, by creating overview tables. MAIN RESULTS: For this update, we screened 1645 publications of which 45 met the inclusion criteria (20 additional studies to the previous reviews). In total, we analysed data from 18 drugs and 4696 participants. There was a very high degree of statistical and clinical heterogeneity in the trials and we discuss the reasons for this in the review. There were some sources of potential bias in the included studies, including a lack of description of the methods of blinding and allocation concealment, and the small size of the study populations. We included studies investigating pemoline and modafinil in participants with multiple sclerosis (MS)-associated fatigue and methylphenidate in patients suffering from advanced cancer and fatigue in meta-analysis. Treatment results pointed to weak and inconclusive evidence for the efficacy of amantadine, pemoline and modafinil in multiple sclerosis and for carnitine and donepezil in cancer-related fatigue. Methylphenidate and pemoline seem to be effective in patients with HIV, but this is based only on one study per intervention, with only a moderate number of participants in each study. Meta-analysis shows an estimated superior effect for methylphenidate in cancer-related fatigue (standardised mean difference (SMD) 0.49, 95% confidence interval (CI) 0.15 to 0.83). Therapeutic effects could not be described for dexamphetamine, paroxetine or testosterone. There were a variety of results for the secondary outcomes in some studies. Most studies had low participant numbers and were heterogeneous. In general, adverse reactions were mild and had little or no impact. AUTHORS' CONCLUSIONS: Based on limited evidence, we cannot recommend a specific drug for the treatment of fatigue in palliative carepatients. Fatigue research in palliative care seems to focus on modafinil and methylphenidate, which may be beneficial for the treatment of fatigue associated with palliative care although further research about their efficacy is needed. Dexamethasone, methylprednisolone, acetylsalicylic acid, armodafinil, amantadine and L-carnitine should be further examined. Consensus is needed regarding fatigue outcome parameters for clinical trials.

3. Hatano Y.

OBJECTIVES: Loss of appetite is prevalent in palliative care and distressing for patients and families. Therapies include corticosteroids or progestogens. This study explores the net effect of dexamethasone on anorexia. METHODS: Prospective data were collected when dexamethasone was started for anorexia as part of routine care. The National Cancer Institutes Common Toxicity Criteria for Adverse Events (NCICTCAE) Likert scales assessed severity of anorexia and immediate and short-term harms at 2 time points: baseline and 7 days. RESULTS: This study (41 sites, 8 countries) collected data (July 2013 to July 2014) from 114 patients (mean age 71 (SD 11), 96% with cancer). Median Australian-modified Karnofsky Performance Scale was 50% (range 20-70). Mean baseline NCICTCAE anorexia score was 2.7 (SD 0.6; median 3). 6 patients died by day 7. Of 108 evaluable patients, 74 (68.5%; 95% CI 59.0% to 76.7%) reported ≥1 reduction anorexia scores by day 7, of whom 30 were 0. Mean dexamethasone dose on day 7 was 4.1 mg/day (SD 3.4; median 4; range 0-46 mg). 24 patients reported ≥1 harms

(32.4% CI 22.6% to 44.1%; insomnia n=10, depression n=7, euphoria n=7 and hyperglycaemia n=7). Of 24 patients with no benefit, 10 reported ≥1 harms. CONCLUSIONS: This study shows positive and negative effects of 7 days of dexamethasone as an appetite stimulant in patients with advanced life-limiting illnesses. Identifying clinicodemographic characteristics of people most at risk of harms with no benefit is a crucial next step. Longer term follow-up will help to understand longer term and cumulative harms.

4. Tanguy-Goarin C.

Drugs delivery by subcutaneous injection is often the last resort/appeal for a doctor anxious to limit the aggressive and invasive treatments, particularly within palliative care. A review was made to list the drugs which can be administered by this route. Concerned antibiotics are teicoplanin, netilmicin and gentamicin with a risk of skin necrosis for aminoglycosids. Midazolam is useful in various indications and can be associated with morphine in case of dyspnoea. Data about subcutaneous injection of dexamethasone, clonazepam, haloperidol and levomepromazine are published; it is the same for fentanyl, nefopam, ondansetron and metoclopramide. The subcutaneous injection of these quoted drugs is possible, but requires further studies.

5. Walker J.

Searching for good evidence to develop clinical practice guidelines can be challenging, as research may not be published or available. A simple question set the authors on a journey to find evidence related to the nursing afministration of subcutaneous dexamethasone in the palliative setting. This article outlines the search for evidence and discusses the survey results to gather expert opinion about the nursing administration of dexamethasone. Survey results indicated that only 39% of community services gave dexamethasone via a bolus injection and 88% gave it via a continuous infusion, mainly for site preservation. The diluents used were water for injection or normal saline. Many procedural aspects were supported by current guidelines, with several services using the New Zealand Waitemata District Health Board's (2008) clinical guidelines. Developing and implementing procedural recommendations for nurses to administer this subcutaneous medication will form the next stage of the project.

4.4. GABAPENTIN

USO *OFF-LABEL* CHE SI VUOLE AUTORIZZARE:

1. Somministrazione per trattamento del **dolore neuropatico**

RAZIONALE DELLA RICHIESTA:

I farmaci antiepilettici sono frequentemente usati nella terapia del dolore neuropatico. Il gabapentin è un antiepilettico che negli ultimi anni si è imposto come uno dei farmaci più frequentemente impiegati nella terapia del dolore neuropatico. Il dosaggio abitualmente utilizzato è di "600 mg", titolabile fino a "3600 mg" al dì in base alla risposta antalgica ottenuta. Il sintomo dolore è frequente nelle fasi avanzate di patologie neoplastiche e non. Inoltre, la presenza del dolore neuropatico è talora concomitante al dolore nocicettivo, come accade per esempio nelle fasi avanzate di alcune malattie neurodegenerative, per la presenza di spasticità, o in quelle neoplastiche, per l'infiltrazione della massa tumorale nelle strutture limitrofe (oltre a quelle nervose). Il gabapentin ha attualmente tra le sue indicazioni anche quella per il trattamento del dolore neuropatico, grazie alla sua capacità di inibire il rilascio di neurotrasmettitori che promuovono appunto la trasmissione del sintomo dolore. Tuttavia, la sua autorizzazione è limitata al trattamento del dolore neuropatico periferico, in corso di neuropatia diabetica dolorosa o nevralgia post-herpetica. Nonostante il trattamento del dolore neuropatico sia trattabile anche con altri prodotti già autorizzati (ad esempio, tra i triciclici l'amitriptilina è indicata per il dolore neuropatico periferico dell'adulto, e tra i gli antiepilettici il pregabalin è indicato per il trattamento del dolore neuropatico periferico e centrale negli adulti), consentirne il trattamento anche con gabapentin, permetterebbe di scegliere il trattamento migliore considerando le peculiarità del paziente, gli effetti collaterali dei vari farmaci (v. le numerose severe reazioni avverse dei triciclici), l'interazione con le terapie concomitanti e i costi.

SITUAZIONE ATTUALE APPROVATA:

Compresse da 100, 300 e 400 mg: trattamento di attacchi epilettici parziali in presenza o in assenza di generalizzazione secondaria e del dolore neuropatico periferico quale la neuropatia diabetica dolorosa e la nevralgia post-herpetica.

RICERCA BIBLIOGRAFICA RICHIESTA:

Parole chiave: Gabapentin, neuropathic cancer pain

Lavori evidenziati:

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RCT DISPONIBILI:

Sì, abstract 1

ABSTRACT RICHIESTA:

1. Caraceni A.

Purpose To determine the analgesic effect of the addition of gabapentin to opioids in the management of neuropathic cancer pain. Patients and Methods One hundred twenty-one consecutive patients with neuropathic pain due to cancer, partially controlled with systemic opioids, participated in a multicenter, randomized, double-blind, placebo-controlled, parallel-design, 10-day trial from August 1999 to May 2002. Gabapentin was titrated from 600 mg/d to 1,800 mg/d in addition to stable opioid dose. Extra opioid doses were available as needed. Zero to 10 numerical scale was used to rate average daily pain. The average pain score over the whole follow-up period was used as main outcome measure. Secondary outcome measures were: intensity of burning pain, shooting/lancinating pain, dysesthesias (also scored on 0 to 10 numerical scale), number of daily episodes of lancinating pain, presence of allodynia, and daily extra doses of opiod analgesics. Results Overall, 79 patients received gabapentin and 58 (73%) completed the study; 41 patients received placebo and 31 (76%) completed the study. Analysis of covariance (ANCOVA) on the intent-to-treat population showed a significant difference of average pain intensity between gabapentin (pain score, 4.6) and placebo group (pain score, 5.4; *P* _ .0250). Among secondary outcome measures, dysesthesia score showed a statistically significant difference (*P* _ .0077; ANCOVA on modified intent-to-treat population _ 115 patients with at least 3 days of pain assessments). Reasons for withdrawing patients from the trial were adverse events in six patients (7.6%) receiving gabapentin and in three patients receiving placebo (7.3%). Conclusion Gabapentin is effective in improving analgesia in patients with neuropathic cancer pain already treated with opioids.

2. Matthew T.

Neuropathic pain is notoriously variable in its severity and impact on patients, as well as in its response to treatment. Certain therapies for neuropathic pain have better evidence for their use; however, it is apparent that although some therapies provide relief for only a minority of patients, the relief may be significant. Without a trial of therapy, there is no way to know if that relief is achievable. Our treatment experiences have shown that occasionally unexpected benefit is obtained through a thorough investigation of all options, even in the setting of failure of those with the most compelling evidence or indication.

Chronic neuropathic pain is generally best treated with regularly dosed medications, balancing efficacy and tolerability. Evidence supports first-line trials of anticonvulsants, tricyclic antidepressants, and serotonin-norepinephrine reuptake inhibitors, alone or in certain combinations. While opioid medications, particularly methadone, can be effective in treating neuropathic pain, they are best used only in refractory cases and by experienced clinicians, due to concerns for both short- and long-term safety. Some therapies have a long history of successful use for certain syndromes (e.g., carbamazepine for trigeminal neuralgia pain), but these should not be considered to the exclusion of other more recent, less-supported therapies (e.g., botulinum toxin A for the same), particularly in refractory cases. We find the principles of palliative care highly applicable in the treatment of chronic neuropathic pain, including managing expectations, mutually agreed-upon meaningful outcomes, and a carefully cultivated therapeutic relationship.

3. Deng J.

Background The management of neuropathic pain (NP) is challenging despite it being the recent focus of extensive research. A number of clinical practice guidelines (CPGs) for the management of NP have been published worldwide over the past 2 decades. This study aimed to assess the quality of these CPGs. Methods We performed a systematic review of published CPGs for the management of NP. Three reviewers independently assessed the quality of the CPGs using the Appraisal of Guidelines Research and Evaluation II (AGREE-II) instrument, and recommendations of CPGs were also appraised. Results A total of 16 CPGs were included. Thirteen CPGs were developed using an evidence-based approach, and the remaining CPGs were produced by consensus panels. None of CPGs obtained a score greater than 50 % in all six AGREE II instrument domains mainly owing to poor performance in the “Applicability” domain. The highest score of the CPGs was achieved in “Clarity and Presentation” domain, followed by “Scope and Purpose” and “Editorial Independence” domains, and the lowest scores were found the in “Applicability” domain. The majority of the CPG recommendations on the management of patients with NP were relatively consistent, especially regarding the recommendation of stepwise treatment with medication. Conclusions Greater efforts are needed not only to improve the quality of development and presentation of the CPGs, but also to provide more efficacy evidence for the management of patients with NP.

4. Keskinbora K.

Neuropathic cancer pain represents a major challenge. Treatment often requires adjuvant analgesics, including gabapentin, to complement the effects of opioids. This study aimed to compare the effectiveness and safety of gabapentin combined with an opioid versus opioid monotherapy for the management of neuropathic cancer pain. Seventy-five cancer patients who were receiving opioid therapy and reported sufficient pain relief of nociceptive, but not neuropathic, pain were enrolled. Sixty-three patients completed the study. Patients were randomized to one of the following treatment protocols: 1) gabapentin adjuvant to ongoing opioid treatment titrated according to pain response while opioid dose was kept constant (group GO), and 2) continuation of opioid monotherapy according to the World Health Organization treatment ladder approach (group OO). Changes in pain intensity, allodynia, and analgesic drug consumption were evaluated at Day 4 and Day 13.

Side effects were also recorded. Both treatments resulted in a significant reduction of pain intensity at Day 4 and Day 13 compared to baseline. However, mean pain intensity for burning and shooting pain was significantly higher in the OO group compared to the GO group at both the fourth (P ¼ 0.0001) and 13th (P ¼ 0.0001) days of the study. An earlier significant decrease (at Day 4, P ¼ 0.002) was observed for allodynia in the GO group compared to the OO group. The rate of side effects in the GO group was significantly lower than that in the OO group (P ¼ 0.015). These data suggest that gabapentin added to an opioid provides better relief of neuropathic pain in cancer patients than opioid monotherapy; this combination of gabapentin and an opioid may represent a potential first-line regimen for the management of pain in these patients.

4.5. METOCLOPRAMIDE

USO *OFF-LABEL* CHE SI VUOLE AUTORIZZARE:

1. Somministrazione EV/SC per **nausea e vomito**, **occlusione intestinale incompleta**, **anoressia da gastroparesi** nei pazienti in cure palliative con breve aspettativa di vita (presumibile < 3 mesi) anche per periodi superiori a 5 giorni, se il beneficio atteso supera il rischio.
2. Somministrazione EV/SC per **singhiozzo** nei pazienti in cure palliative con breve aspettativa di vita (presumibile < 3 mesi) anche per periodi superiori a 5 giorni, se il beneficio atteso supera il rischio.

RAZIONALE DELLA RICHIESTA:

1. **Nausea e vomito** sono sintomi comuni e fastidiosi per i pazienti che affrontano la fase terminale della vita (prevalenza fino al 70% nelle malattie oncologiche) e hanno un pesante impatto sulla qualità della vita. Metoclopramide è utilizzata dagli anni ’60 per il trattamento della nausea e del vomito da cause diverse e per i disturbi della motilità gastrica e oggi rappresenta il farmaco procinetico più diffuso e disponibile. Metoclopramide rappresenta pertanto uno dei farmaci di prima scelta nel trattamento antiemetico e viene inoltre inclusa nella lista dei farmaci essenziali in cure palliative per il trattamento di nausea e vomito, rappresentando il farmaco di prima scelta nel trattamento di molte situazioni ricorrenti nel *setting* di cure palliative quali nausea e vomito, occlusione intestinale incompleta, anoressia da gastroparesi. La scelta di questo principio attivo è giustificata anche dal fatto che è ben tollerato, è meno costoso rispetto ad altre opzioni terapeutiche e, al momento, non sono disponibili alternative per i pazienti critici. La scheda tecnica del farmaco prevede inoltre il suo utilizzo esclusivamente per via endovenosa o intramuscolare, ma la via di somministrazione maggiormente utilizzata in cure palliative è quella sottocutanea, come riportato da ampie evidenze in letteratura e tale possibilità viene riportata anche in “Guida all’uso dei farmaci” dell’AIFA. I dosaggi riportati in letteratura vanno da un minimo di 30 mg per os a 120 mg EV/SC nelle 24 ore, è prevista una titolazione ed in rapporto alla valutazione rischi/benefici il trattamento può essere protratto oltre i cinque giorni.
2. Il **singhiozzo** rappresenta uno dei sintomi più fastidiosi per i pazienti con malattia in fase avanzata. Il singhiozzo può essere un evento singolo, ma in alcuni pazienti può protrarsi per ore o giorni con un pesante impatto sulla qualità della vita, sulla possibilità di alimentazione, sul sonno e sul tono dell’umore. In caso di singhiozzo persistente è importante ricercarne le cause, ma non sempre, nel paziente oncologico in fase avanzata, è possibile individuarle ed agire su di esse e diviene pertanto prioritario cercare di raggiungere un adeguato controllo del sintomo. La metoclopramide in queste situazioni, somministrata per via EV/SC al dosaggio di 10-20 mg 3-4 volte al dì, rappresenta uno dei farmaci di prima scelta.

SITUAZIONE ATTUALE APPROVATA:

- Compresse e soluzione orale: prevenzione di nausea e vomito ritardati indotti da chemioterapia (CINV); prevenzione di nausea e vomito indotti da radioterapia (RINV); trattamento sintomatico di nausea e vomito, inclusi nausea e vomito indotti da emicrania acuta.
- Soluzione iniettabile: per la prevenzione della nausea e del vomito che possono manifestarsi dopo interventi chirurgici; per la prevenzione della nausea e del vomito provocati da radioterapia; per il trattamento della nausea e del vomito, compresi nausea e vomito che possono accompagnare un'emicrania acuta.

RICERCA BIBLIOGRAFICA RICHIESTA 1:

Parole chiave: metoclopramide, nausea, vomiting, bowel obstruction, palliative care

Lavori evidenziati:

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9. P. A. Glare, D. Dunwoodie, K. Clark et al. Treatment of Nausea and Vomiting in Terminally Ill Cancer Patients. Drugs. 2008;68(18):2575-90.

RICERCA BIBLIOGRAFICA RICHIESTA 2:

Parole chiave: metoclopramide, hiccups, palliative care

Lavori evidenziati:

1. Madanagopolan N. Metoclopramide in hiccup. Curr Med Res Opin. 1975;3(6):371-4.
2. Moretto EN, Wee B. et al. Interventions for treating persistent and intractable hiccups in adults (review). The Cochrane Library 2013, Issue 1
3. Wang T, Wang D. Metoclopramide for patients with intractable hiccups: a multicentre, randomised, controlled pilot study. Intern Med J. 2014 Dec;44(12a):1205-9.
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NOTE:

Nel 2013 l'European Medicines Agency (EMA) ha richiamato l'attenzione sulla molecola a causa di effetti avversi neurologici (sintomi extrapiramidali e discinesia tardiva) e cardiaci (disturbi della conduzione) più frequenti soprattutto per trattamenti prolungati, a dosaggi elevati e in pazienti in età geriatrica. Per tale motivo il dosaggio massimo è stato fissato a 30 mg/die, la durata del trattamento è stata ridotta a 5 giorni e le indicazioni sono state limitate a prevenzione e trattamento a breve termine di nausea e vomito associati a chemioterapia, radioterapia, interventi chirurgici ed emicrania. Il rischio di discinesia tardiva, l'effetto collaterale più frequente nell'utilizzo prolungato del farmaco, è inferiore al 1%, decisamente inferiore al 10% riportato in alcune linee guida. Numerose linee guida e studi clinici propongono di non estendere queste indicazioni ai pazienti in cure palliative e la stessa EMA, per voce del dr. Paul Blake del Committee for Medicinal Products for Human Use (CHMP), ha affermato che raccomandazioni del CHMP sono basate su un'attenta analisi delle prove per l'efficacia e la sicurezza di metoclopramide per le indicazioni autorizzate. Dal momento che l'uso in cure palliative non era un'indicazione riportata in scheda tecnica, la valutazione del CHMP non ha esaminato specificamente tale utilizzo. Lo scopo della revisione è stato quello di esaminare le prove per l'efficacia e la sicurezza nelle indicazioni autorizzate e di limitare l'uso di metoclopramide a quelle per le quali esistevano prove attendibili che dimostravano un rapporto beneficio-rischio favorevole. In cure palliative si ricorre spesso all'uso di farmaci per indicazioni differenti a quanto indicato in scheda tecnica, poiché nei pazienti in fase terminale di malattia il rapporto tra rischi e benefici può differire da altri gruppi di pazienti. Presumibilmente, anche se le indicazioni autorizzate per l'uso di metoclopramide sono limitate, qualora l'uso *off-label* di metoclopramide sia stato precedentemente riconosciuto come pratica standard da specialisti in cure palliative, ciò non deve necessariamente cambiare in conseguenza alla revisione fatta dal CHMP. In teoria, quindi, non vi è alcuna ragione per cui i cambiamenti nelle informazioni su metoclopramide dovrebbero impedire l'uso del farmaco nelle situazioni per le quali lo stesso viene abitualmente utilizzato in cure palliative.

ABSTRACT RICHIESTA 1:

1. Davis MP

CONTEXT: A systematic review of antiemetics for emesis in cancer unrelated to chemotherapy and radiation is an important step in establishing treatment

recommendations and guiding future research. Therefore, a systematic review based on the question "What is the evidence that supports antiemetic choices in advanced cancer?" guided this review. OBJECTIVES: To determine the level of evidence for antiemetics in the management of nausea and vomiting in advanced cancer unrelated to chemotherapy and radiation, and to discover gaps in the evidence, which would provide important areas for future research. METHODS: Three databases and independent searches using different MeSH terms were performed. Related links were searched and hand searches of related articles were made. Eligible studies included randomized controlled trials (RCTs), prospective single-drug studies, studies that used guidelines based on the etiology of emesis, cohort studies, retrospective studies, and case series or single-patient reports. Studies that involved treatment of chemotherapy, radiation, or postoperation-related emesis were excluded. Studies that involved the treatment of emesis related to bowel obstruction were included. The strength of evidence was graded as follows: 1) RCTs, A; 2) single-drug prospective studies, B1; 3) studies based on multiple drug choices for etiology of emesis, B2; and 4) cohort, case series, retrospective, and single-patient reports, E. Level of evidence was determined by the Oxford Centre for Evidence-Based Medicine Levels of Evidence (May 2001) (A, B, C, D). RESULTS: Ninety-three articles were found. Fourteen were RCTs, most of them of low quality, based either on lack of blinding, lack of description of the method of randomization, concealment, and/or attrition. Metoclopramide had modest evidence (B) based on RCTs and prospective cohort studies. Octreotide, dexamethasone, and hyoscine butylbromide are effective in reducing symptoms of bowel obstruction, based on prospective studies and/or one RCT. There was no evidence that either multiple antiemetics or antiemetic choices based on the etiology of emesis were any better than a single antiemetic. There is poor evidence for dose response, intraclass or interclass drug switch, or antiemetic combinations in those individuals failing to respond to the initial antiemetic. CONCLUSION: There are discrepancies between antiemetic studies and published antiemetic guidelines, which are largely based on expert opinion. Antiemetic recommendations have moderate to weak evidence at best. Prospective randomized trials of single antiemetics are needed to properly establish evidence-based guidelines.

2. Bruera E.

The purpose of this retrospective study is to assess the frequency and intensity of chronic nausea in patients admitted to the Palliative Care Unit and the results of a metoclopramide-based treatment regimen. We reviewed the medical records of 100 consecutive patients admitted to the Palliative Care Unit at the Edmonton General Hospital until death during 1992-1993. All patients had terminal cancer and normal cognitive function. All patients completed the Functional Analogue Scale for appetite, nausea, pain, activity, shortness of breath, and sensation of well-being at 1000 and 1600 hours every day. Patients who complained of nausea initially received metoclopramide 10 mg every 4 hr orally or subcutaneously (Step 1). If nausea persisted, dexamethasone 10 mg twice daily was added (Step 2). Step 3 consisted of a continuous subcutaneous infusion of metoclopramide of 60-120 mg/day plus dexamethasone. If no response was observed, other antiemetics were administered (Step 4). Upon admission to the unit, 32 patients (32%) presented with nausea. During the average admission of 25 +/- 13 days, 98 patients (98%) developed nausea. Twenty-five patients (25%) required other antiemetics because of bowel obstruction (18), extrapyramidal side effects (3), or other reasons (4). Most patients without bowel obstruction achieved excellent control of nausea

using the metoclopramide-based regimen. During the first 5 days and last 5 days of admission, nausea had significantly lower intensity than the rest of the symptoms that were monitored. Our results suggest that, although nausea is very frequent, it can be well controlled in the majority of patients using safe and simple antiemetic regimens.

3. Walsh D.

PURPOSE: The aim of this paper is to review the existing literature related to the management of nausea and vomiting (N & V) in advanced cancer and derive clinical evidence-based recommendations for its management. METHODS: Available systematic reviews on antiemetic drug effectiveness were used. One generic systematic review of antiemetics in advanced cancer (to 2009) was updated to February 2016. Agreement on recommendations was reached between panel members, and these were voted in favor unanimously by the larger antiemetic committee membership (n = 37). RESULTS: The evidence base in this field is minimal with largely poor quality trials or uncontrolled trials and case studies. The level of evidence in most studies is low. The drug of choice for managing N & V in advanced cancer is metoclopramide titrated to effect. Alternative options include haloperidol, levomepromazine, or olanzapine. For bowel obstruction, the recommendation is to use octreotide given alongside an antiemetic (haloperidol) and where octreotide is not an option to use an anticholinergic antisecretory agent. For opioid-induced N & V, no recommendation could be made. CONCLUSION: These new guidelines, based on the existing (but poor) evidence, could help clinicians manage more effectively the complex and challenging symptoms of N & V in advanced cancer.

4. Y Gert van der Meer

Regulatory agencies in North America and Europe recently re-evaluated the safety of metoclopramide. This re-evaluation resulted in recommendations and restrictions in order to minimise the risk of neurological and other adverse reactions associated with the use of metoclopramide. In the ICU, off-label prescription of metoclopramide is common. We have reviewed the evidence for safety, effectiveness and dosing of metoclopramide in critically ill patients. Furthermore, tachyphylaxis is addressed and alternatives are summarised. Finally, recommendations are presented not to abandon use of metoclopramide in ICU patients, because metoclopramide is considered effective in enhancing gastric emptying and facilitating early enteral nutrition.

5. Gupta M.

Nausea and vomiting are common and distressing symptoms in advanced cancer. Both are multifactorial and cause significant morbidity, nutritional failure, and reduced quality of life. Assessment includes a detailed history, physical examination and investigations for reversible causes. Assessment and management will be influenced by performance status, prognosis, and goals of care. Several drug classes are effective with some having the added benefit of multiple routes of administration. It is our institution's practice to recommend metoclopramide as the first drug with haloperidol as an alternative antiemetic.

Dexamethasone should be used for patients with central nervous system metastases or bowel obstruction. If your patient is near death, empiric metoclopramide, haloperidol or chlorpromazine is used without further investigation. For patients with a better prognosis, we exclude reversible causes and use the same first-line antiemetics, metoclopramide and haloperidol. For those who do not respond to first-line single antiemetics, olanzapine is second line and ondansetron is third. Rarely do we use combination therapy or cannabinoids. Olanzapine as a single agent has a distinct advantage over antiemetic combinations. It improves compliance, reduces drug interactions and has several routes of administration. Antiemetics, anticholinergics, octreotide and dexamethasone are used in combination to treat bowel obstruction. In opiod-na'ive patients, we prefer haloperidol, glycopyrrolate and an opioid as the first-line treatment and add or substitute octreotide and dexamethasone in those who do not respond. Non-pharmacologic interventions (mechanical stents and percutaneous endoscopic gastrostomy tubes) are used when nausea is refractory to medical management or for home-going management to relieve symptoms, reduce drug costs and rehospitalization.

6. Berger J.

BACKGROUND:Malignant bowel obstruction is a highly symptomatic, often recurrent, and sometimes refractory condition in patients with intra-abdominal tumor burden. Gastro-intestinal symptoms and function may improve with anti-inflammatory, anti-secretory, and prokinetic/anti-nausea combination medical therapy. OBJECTIVE:To describe the effect of octreotide, metoclopramide, and dexamethasone in combination on symptom burden and bowelfunction in patients with malignant bowel obstruction and dysfunction. DESIGN:A retrospective case series of patients with malignant bowel obstruction (MBO) and malignant bowel dysfunction (MBD) treated by a palliative care consultation service with octreotide, metoclopramide, and dexamethasone. Outcomes measures were nausea, pain, and time to resumption of oral intake. RESULTS:12 cases with MBO, 11 had moderate/severe nausea on presentation. 100% of these had improvement in nausea by treatment day #1. 100% of patients with moderate/severe pain improved to tolerable level by treatment day #1. The median time to resumption of oral intake was 2 days (range 1-6 days) in the 8 cases with evaluable data. Of 7 cases with MBD, 6 had For patients with malignant boweldysfunction, of those with moderate/severe nausea. 5 of 6 had subjective improvement by day#1. Moderate/severe pain improved to tolerable levels in 5/6 by day #1. Of the 4 cases with evaluable data on resumption of PO intake, time to resume PO ranged from 1-4 days. CONCLUSION:Combination medical therapy may provide rapid improvement in symptoms associated with malignant bowel obstruction and dysfunction.

7. Emily Collis

A recent review by the European Medicines Agency and Medicines and Healthcare products Regulatory Agency concluded that the risks of neurological effects with metoclopramide such as extrapyramidal disorders and tardive dyskinesia outweigh the benefits in long term or high dose treatment. Recommended used for short period (5 days) at maximum dose of 30 mg/24 hours. In practice sometimes used for longer durations and higher doses in palliative care but only if benefit outweighs risk.

8. Bruera E.

The purpose of this retrospective study is to assess the frequency and intensity of chronic nausea in patients admitted to the Palliative Care Unit and the results of a metoclopramide-based treatment regimen. We reviewed the medical records of 100 consecutive patients admitted to the Palliative Care Unit at the Edmonton General Hospital until death during 1992-1993. All patients had terminal cancer and normal cognitive function. All patients completed the Functional Analogue Scale for appetite, nausea, pain, activity, shortness of breath, and sensation of well-being at 1000 and 1600 hours every day. Patients who complained of nausea initially received metoclopramide 10 mg every 4 hr orally or subcutaneously (Step 1). If nausea persisted, dexamethasone 10 mg twice daily was added (Step 2). Step 3 consisted of a continuous subcutaneous infusion of metoclopramide of 60-120 mg/day plus dexamethasone. If no response was observed, other antiemetics were administered (Step 4). Upon admission to the unit, 32 patients (32%) presented with nausea. During the average admission of 25 +/- 13 days, 98 patients (98%) developed nausea. Twenty-five patients (25%) required other antiemetics because of bowel obstruction (18), extrapyramidal side effects (3), or other reasons (4). Most patients without bowel obstruction achieved excellent control of nausea using the metoclopramide-based regimen. During the first 5 days and last 5 days of admission, nausea had significantly lower intensity than the rest of the symptoms that were monitored. Our results suggest that, although nausea is very frequent, it can be well controlled in the majority of patients using safe and simple antiemetic regimens.

9. Glare PA

Nausea and vomiting is a common and distressing symptom complex in patients with far-advanced cancer, affecting up to 60% of individuals at some stage of their illness. The current approach to the palliative care of patients with nausea and vomiting is based on identifying the cause, understanding its pathophysiology and knowing the pharmacology of the drugs available for its amelioration. The following six main syndromes are identified: gastric stasis, biochemical, raised intracranial pressure, vestibular, mechanical bowel obstruction and ileus. A careful history, focused physical examination and appropriate investigations are needed to elucidate the syndrome and its cause, so that therapy is rational. Drugs are the mainstay of treatment in terminal cancer, and the main classes of antiemetic agents are prokinetics, dopamine antagonists, antihistamines, anticholinergics and serotonin antagonists. Dexamethasone and octreotide are also used, especially in bowel obstruction. Non-drug measures are important in relieving the associated distress. Patients should be able to die comfortably, without tubes. Despite decades of practice affirming this approach, the evidence base is weak and well designed studies are urgently needed.

ABSTRACT RICHIESTA 2:

1. Madanagopolan N

Metaclopramide has been observed to induce dramatic relief of intractable hiccup in 14 patients with diverse serious illnesses. When given orally or parenterally the effect was observed within 30 minutes, the relief lasting up to 8 hours, indicating a direct relation to the duration of action of the drug. This drug is recommended for symptomatic relief of hiccup associated even with serious organic illnesses, without any fear of undesirable effects.

2. Moretto EN

BACKGROUND:Persistent and intractable hiccups (typically defined as lasting for more than 48 hours and one month respectively) can be of serious detriment to a patient's quality of life, although they are relatively uncommon. A wide range of pharmacological and non-pharmacological interventions have been used for the treatment of persistent and intractable hiccups. However, there is little evidence as to which interventions are effective or harmful. OBJECTIVES:The objective of this review was to evaluate the effectiveness of pharmacological and non-pharmacological interventions used in the treatment of persistent and intractable hiccups of any aetiology in adults. SEARCH METHODS: Studies were identified from the following databases: CENTRAL, CDSR, DARE, MEDLINE, EMBASE, CINAHL, PsychINFO and SIGLE (last search March 2012). The search strategy for all the databases searched was based on the MEDLINE search strategy presented in Appendix 1. No additional handsearching of journals was undertaken. Investigators who are known to be carrying out research in this area were contacted for unpublished data or knowledge of the grey literature. SELECTION CRITERIA:Studies eligible for inclusion in this review were randomised controlled trials (RCTs) or controlled clinical trials (CCTs). INCLUSION CRITERIA:adults (over 18 years old) diagnosed with persistent or intractable hiccups (hiccups lasting more than 48 hours), treated with any pharmacological or non-pharmacological intervention. EXCLUSION CRITERIA:less than ten participants; no assessment of change in hiccup frequency or intensity in outcome measures. DATA COLLECTION AND ANALYSIS:Two independent review authors assessed each abstract and title for relevance. Disagreement on eligibility was resolved by discussion. Where no abstract was available the full paper was obtained and assessed. We obtained full copies of the studies which met the inclusion criteria for further assessment. Two review authors independently collected data from each appropriate study and entered them into the software Review Manager 5. Two independent review authors assessed the risk of bias using the RevMan 5 'Risk of bias' table following guidance from the Cochrane Handbook of Systematic Reviews of Interventions (Higgins 2009). MAIN RESULTS: A total of four studies (305 participants) met the inclusion criteria. All of these studies sought to determine the effectiveness of different acupuncture techniques in the treatment of persistent and intractable hiccups. All four studies had a high risk of bias, did not compare the intervention with placebo, and failed to report side effects or adverse events for either the treatment or control groups. Due to methodological differences we were unable to perform a meta-analysis of the results. No studies investigating pharmacological interventions for persistent and intractable hiccups met the inclusion criteria. AUTHORS' CONCLUSIONS:There is insufficient evidence to guide the treatment of persistent or intractable hiccups with either

pharmacological or non-pharmacological interventions.The paucity of high quality studies indicate a need for randomised placebo-controlled trials of both pharmacological and non-pharmacological treatments. As the symptom is relatively rare, trials would need to be multi-centred and possibly multi-national.

3. Wang T

BACKGROUND: Limited data exist regarding the efficacy of metoclopramide in the treatment of intractable hiccups. AIM:This study aimed to assess the feasibility efficacy of metoclopramide in the treatment of patients with intractable hiccups. METHODS:A total of 36 patients with intractable hiccups was randomly assigned to arm A (n = 18) or arm B (n = 18) in a multicentre, double-blind, randomised, controlled pilot study. Participants in arm A received 10-mg metoclopramide thrice daily for 15 days, whereas those assigned to arm B received 10-mg placebo thrice daily for 15 days. The primary outcome measure was total efficacy against hiccups (including cessation and improvement of hiccups). Secondary outcome measures included a comparison of overall efficacy and adverse events between the two arms. RESULTS: Of the 36 patients enrolled, 34 participants completed the study. The total efficacy was higher in arm A than in arm B (relative risk, 2.75; 95% confidence interval: 1.09-6.94, P = 0.03). Furthermore, comparison between the two arms revealed that overall efficacy was higher in arm A than that in arm B (P < 0.05). No serious adverse events related to the treatment were documented in either arm. The most common adverse events occurring in patients in arm A included fatigue, upset mood and dizziness. CONCLUSION: Metoclopramide appears to be a promising candidate for the treatment of patients with intractable hiccups, with mild adverse events. However, further clinical trials are required to confirm these results.

4. Jeon YS

Persistent hiccups are a frustrating experience for palliative care patients, and can have a profound impact on their quality of life. This article provides an evidence-based approach overview of the causes and treatment of this not infrequently debilitating condition for such patients, with a management algorithm. In situations where no readily reversible cause is identified, or where simple physical manoeuvres, such as breath holding have failed, a systematic approach is required. Hiccups can be broadly divided into central and peripheral types. These respond differently to pharmacological intervention. The drug of choice for central causes of persistent hiccups is baclofen, with metoclopramide recommended as the first choice for peripheral causes. Midazolam may be useful in cases of terminal illness. Interventional procedures such as vagal or phrenic nerve block or stimulation should be considered in patients who are refractory to medications. The management of persistent hiccups still presents an ongoing clinical challenge however, requiring further research on pathophysiology and treatment strategies. Multinational randomised controlled trials to evaluate and compare both current and new medications or procedures to better manage this difficult condition are suggested as a means of reaching this goal.

4.6. MIDAZOLAM

USO *OFF-LABEL* CHE SI VUOLE AUTORIZZARE:

1. Somministrazione EV/IM/SC/OS per **agitazione psicomotoria/delirium** nei pazienti in fase terminale.
2. Somministrazione EV/IM/SC per **convulsioni** in pazienti in fase terminale.
3. Somministrazione SC/IM per **sedazione periprocedurale** (es.: durante manovre terapautiche/assistenziali) in pazienti in fase avanzata di malattia e non in fase di terminalità. Viene quindi richiesta l'autorizzazione all'impiego della via sottocutanea e intramuscolare.
4. Somministrazione EV/IM/SC per la **sedazione palliativa di tutti i sintomi** che causano angoscia e sofferenza, che non rispondono al trattamento con farmaci specifici, nel paziente terminale. Viene quindi una duplice richiesta sia di autorizzazione all'impiego della via sottocutanea e intramuscolare, sia all'utilizzo del midazolam per il controllo del distress psicofisico indotto da sintomi refrattari (vedi definizione nelle note).

RAZIONALE DELLA RICHIESTA:

1. L'**agitazione psicomotoria/delirium** è una delle più comuni complicazioni neuropsicologiche nei pazienti in fase avanzata di malattia nei pazienti negli ultimi giorni di vita. Il *delirium* è fonte di sofferenza fisica e psichica e crea problemi di gestione clinica e assistenziale, necessitando di un trattamento farmacologico. Ha un'incidenza altissima fino al 39% nel paziente negli ultimi sei mesi di vita, e tra l'80-90% negli ultimi giorni di vita e solo il 50% dei casi di delirium è reversibile. L'effetto sedativo e amnesico e la breve emivita del midazolam, ne fanno un farmaco ideale per il trattamento di questo sintomo; può essere somministrato per via orale, intramuscolare, endovenosa e sottocutanea.
2. Le **convulsioni** in ambito palliativo possono presentarsi per: a) neoplasie primitive dell'encefalo; b) neoplasie secondarie dell'encefalo; c) alterazioni tossico – metaboliche. Si possono manifestare con incompleto recupero clinico nell'intervallo tra di loro: a) crisi parziali; b) crisi generalizzate di tipo tonico-clonico; c) crisi comiziali ravvicinate (con incompleto recupero clinico nell'intervallo fra di loro: almeno 2 crisi in 30 minuti). Hanno un'incidenza relativamente elevata sino al 6% di tutti i malati oncologici indipendentemente dalla localizzazione di malattia. L'effetto sedativo e amnesico e la breve emivita del midazolam, ne fanno un farmaco ideale per il trattamento di questo sintomo.
3. L'utilizzo del midazolam sia a scopo sedativo periprocedurale che sedativo in senso generale è attualmente approvato per via EV, IM e RETTALE, e orale per il preparato Buccolam nel minore. La via sottocutanea è però nell'ambito delle Cure Palliative, la più utilizzata nel paziente in fase avanzata e terminale di malattia perché vantaggiosa dal punto di vista della facilità di reperimento da parte degli operatori delle cure palliative e di utilizzo da parte dei caregiver; permette inoltre, la somministrazione di farmaci anche a malati non collaboranti o per i quali la via per *os* è controindicata o non praticabile. Per questi motivi è ragionevole l'utilizzo del midazolam anche **per via sottocutanea, in bolo o attraverso somministrazione in continuo** sia a scopo

sedativo periprocedurale che in corso di sedazione palliativa per il controllo dei sintomi refrattari (vedi note). Anche la via per *os* è comunque utilizzabile quando percorribile, e lo deve essere anche per i pazienti adulti.

NOTA

L'**Utilizzo domiciliare e extra ospedaliero** del midazolam per il trattamento di pazienti in fase avanzata e terminale di malattia in regime domiciliare, sotto la responsabilità medica, costituisce elemento fondamentale nel percorso di cura di questi malati. Il *setting* di cura domiciliare è infatti previsto dai LEA come un livello assistenziale appropriato. Limitare l'utilizzo del midazolam alle sole strutture ospedaliere o ad esse assimilate, determinerebbe una disparità di trattamento tra pazienti della stessa tipologia e con gli stessi bisogni, anche in considerazione del fatto che il rapporto tra malati in fase terminale di malattia ricoverati in Hospice e pazienti a domicilio è di circa 1:2-4.

SITUAZIONE ATTUALE APPROVATA:

SEDAZIONE COSCIENTE prima e durante procedure diagnostiche o terapeutiche con o senza anestesia locale. Per via EV, IM, Rettale in strutture ospedaliere o ad esse assimilate.

ANESTESIA

– premedicazione prima dell'induzione dell'anestesia. Per via EV, IM, Rettale, in strutture ospedaliere o ad esse assimilate.

– induzione dell'anestesia. Per via EV, in strutture ospedaliere o ad esse assimilate

SEDAZIONE IN UNITÁ DI CURA INTENSIVA. Per via EV, in strutture ospedaliere o ad esse assimilate.

TRATTAMENTO DI CRISI CONVULSIVE ACUTE PROLUNGATE, in bambini e adolescenti (da 3 mesi a < 18 anni). Per via orale deve essere usato solo da genitori/persone che prestano assistenza in pazienti che abbiano ricevuto una diagnosi di epilessia. Per i bambini di età compresa tra 3 e 6 mesi il trattamento deve essere eseguito in contesto ospedaliero, in cui sia possibile il monitoraggio e siano disponibili presidi per la rianimazione.

RICERCA BIBLIOGRAFICA RICHIESTA 1:

Parole chiave: "MIDAZOLAM AND PALLIATIVE CARE"; "MIDAZOLAM DELIRIUM AND AGITATION AND PALLIATIVE CARE"

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Parole chiave: “MIDAZOLAM SEIZURES PALLIATIVE CARE”

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Parole chiave: “PALLIATIVE SEDATION, PRACTICE GUIDELINES, DRUG MONITORING, QUALITY ASSURANCE”MIDAZOLAM AND PALLIATIVE CARE” - “COCHRANE EVIDENCE” - “SUBCUTANEOUS ADMINISTRATION MIDAZOLAM AND PALLIATIVE CARE”

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COMMENTI E CONCLUSIONI:

Le benzodiazepine rappresentano le molecole maggiormente utilizzate, da sole o in associazione con altri farmaci ad azione sul sistema nervoso centrale. Il midazolam è una benzodiazepina con efficacia ansiolitica, anticonvulsiva, miorilassante e sedativa. La sua idoneità in ambito di sedazione è dovuta al suo agire rapido e in genere molto incisivo, ad una estrema maneggevolezza nell’utilizzo, alla pronta reversibilità del suo effetto (se

sospeso) e ad un profilo di tossicità accettabile. L'effetto dopo una singola somministrazione per via venosa, che subentra in 3-5 minuti, è di breve durata. L'emivita del farmaco è breve, anche se si possono riscontrare estreme variabilità interindividuali (1 – 12 h) in base all'età e alla eventuale presenza di disfunzioni epatiche e renali che possono portare ad alterazioni dl metabolismo con conseguenti accumuli indesiderati di farmaco. L'attuale scheda tecnica del farmaco prevede l'utilizzo del midazolam attraverso la via endovenosa, intramuscolare, orale e rettale. La via di somministrazione maggiormente utilizzata in letteratura, soprattutto in cure palliative, è quella sottocutanea (in bolo o in infusione continua) se altra via è impraticabile. Le cause di impraticabilità della via orale possono essere varie tra cui: nausea, disfagia, vomito, problemi intestinali (ostruzioni-resezioni) oppure per impossibilità di deglutire per deficit neurologici o impedimento meccanico del transito. La possibilità di utilizzare il midazolam in cure palliative per via sottocutanea, in bolo o in continuo, è riportata anche nella Guida all'uso dei farmaci dell'Agenzia Italiana del Farmaco (5° Edizione, 229-233, anno 2008).

L'uso nella sedazione palliative e la via di somministrazione sottocutanea sono riportate inoltre nelle Linee Guida ESMO "*Clinical Practice Guidelines for the management of refractory symptoms at the end of life and the use of palliative sedation- N. I. Chernyl et al*" Ann Oncol (2014) 25 (suppl_3): iii143-iii152.

The published literature describing the use of sedation in the management of refractory symptoms at the end of life is anecdotal and refers to the use of opioids, neuroleptics, benzodiazepines, barbiturates and propofol.

Benzodiazepines		
Midazolam [28, 32, 34, 73–78].	Pharmacology	Water soluble, short-acting benzodiazepine. Metabolised to a lipophilic compound that rapidly penetrates the central nervous system. Brief duration of action because of rapid redistribution; therefore, administration by continuous infusion is generally required to maintain a sustained effect.
	Advantages	Rapid onset. Can be administered i.v., s.c. Can be co-administered with morphine or haloperidol.
	Starting dose	0.5–1 mg/h, 1–5 mg as needed
	Usual effective dose	1–20 mg/h
	Adverse effects	Paradoxical agitation, respiratory depression, withdrawal if dose is rapidly reduced after continual infusion, tolerance.
	Antagonist	Flumazenil
Neuroleptics/antipsychotics		

NOTE:

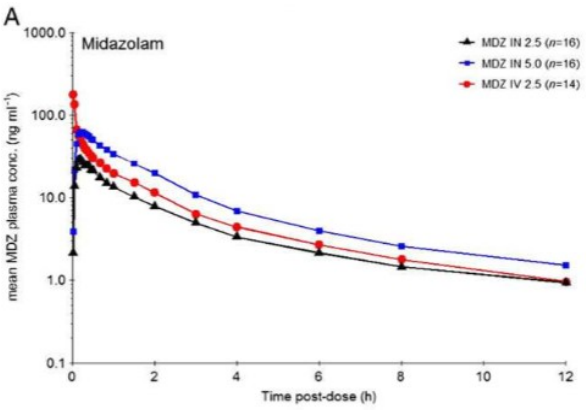
Via Intranasale La somministrazione intranasale delle soluzioni utilizzate IV è molto efficace, ma è sconsigliabile, soprattutto se ripetuta, perché se si usano le soluzioni iniettabili concentrate queste possono, visto il Ph basso, creare bruciore e ulcerazione della mucosa. Una alternativa può essere la diluizione dei preparati disponibili.

Uno studio pubblicato da Schrier L. et al. ("***Pharmacokinetics and pharmacodynamics of a new highly concentrated intranasal midazolam formulation for conscious sedation***") sul Br J Clin Pharmacol. 2017 Apr;83(4):721-731 ha inteso valutare la farmacocinetica, la farmacodinamica, la tolleranza nasale e gli effetti sulla sedazione di una formulazione midazolam intranasale acquosa altamente concentrata (Nazolam) rispetto a midazolam per via endovenosa, su soggetti sani.

La biodisponibilità della formulazione intranasale risulta del 75%. La durata della sedazione è stata di 118 ± 95,6 min per 2,5 mg midazolam per via endovenosa, 76 ± 80,4 min per 2,5 mg Nazolam e 145 ± 104,9 min per 5,0 mg Nazolam. Nazolam inoltre non ha causato danni alla mucosa nasale

Pharmacokinetic parameters of midazolam and α-hydroxy-midazolam in healthy subjects after administration of a single dose of 2.5 mg midazolam intravenous (IV) or 2.5 or 5 mg midazolam intranasal (IN)

	Treatment	$AUC_{0-\infty}$ (ng h ml^{-1})	C_{max} (ng ml^{-1})	$t_{1/2}$(h)	T_{max}(min)	F
Midazolam	Midazolam 2.5 mg IV	93.9 (33.8)	219.2 (68.1)	3.6 (29.4)	2.0 (1.2–3.0)	1
	Midazolam 2.5 mg IN	65.6 (49.0)**	30.6 (42.3)	6.3 (123.4)*	10.9 (6.0–24.0)	0.74 (0.28–1.85)
	Midazolam 5 mg IN	131.9 (26.0)	66.2 (31.5)	4.3 (31.0)	13.8 (9.0–24.0)	0.76 (0.45–1.20)
α-hydroxy-midazolam	Midazolam 2.5 mg IV	15.83 (36.9)	6.1 (37.2)	4.6 (45.5)	14.4 (9.0–21.0)	
	Midazolam 2.5 mg IN	10.9 (54.1)	2.4 (55.5)	5.3 (40.0)	45.4 (24.0–240.0)	
	Midazolam 5 mg IN	24.0 (37.5)	5.3 (34.5)	6.3 (44.2)	50.6 (21.0–121.2)	



Lo studio conclude che concentrazioni clinicamente efficaci possono essere raggiunte in pochi minuti in seguito ad applicazione nasale di midazolam altamente concentrato con effetti comparabili a quelli osservati dopo somministrazione di midazolam IV.

Via Sublinguale

La via sublinguale sembra assimilabile alla via di somministrazione per la quale risulta autorizzato Buccolam poiché di fatto si tratta di assorbimento transmucosale a livello orale. Per il Buccolam la somministrazione descritta è tra gengiva e guancia; tuttavia, la somministrazione a livello sottolinguale sembra non essere descritta non per questioni correlabili a diversa vascolarizzazione, ma a un piu' semplice utilizzo del dispositivo di somministrazione (la siringa potrebbe essere schiacciata tra i denti dai bambini epilettici).

Posologia

La posologia dei prodotti a base di midazolam presenta una elevata interindividualità da 5-1200 mg/die.

Ulteriori informazioni sono riportate successivamente alla tabella.

Indicazioni	**Adulti < 60 anni**	**Adulti ≥ 60 anni / debilitati o con malattie croniche**	**Bambini**
Sedazione conscia	*e.v.* Dose iniziale: 2-2,5 mg Dosi aggiuntive: 1 mg Dose totale: 3,5-7,5 mg	*e.v.* Dose iniziale: 0,5-1 mg Dosi aggiuntive: 0,5-1 mg Dose totale: <3,5 mg	***e.v. in pazienti di età compresa fra 6 mesi e 5 anni*** Dose iniziale: 0,05-0,1 mg/kg Dose totale: <6 mg ***e.v. in pazienti di età compresa fra 6 e 12 anni*** Dose iniziale: 0,025-0,05 mg/kg Dose totale: <10 mg ***rettale > 6 mesi*** 0,3-0,5 mg/kg ***i.m. 1-15 anni*** 0,05-0,15 mg/kg
Premedicazione in Anestesia	*e.v.* ***1-2 mg ripetuti*** *i.m.* 0,07-0,1 mg/kg	*e.v.* ***Dose iniziale: 0,5 mg, da incrementare lentamente secondo necessità*** *i.m.* 0,025-0,05 mg/kg	***rettale > 6 mesi*** 0,3-0,5 mg/kg ***i.m. 1-15 anni*** 0,08-0,2 mg/kg
Induzione dell'anestesia	*e.v.* 0,15-0,2 mg/kg (0,3-0,35 senza premedicazione)	*e.v.* 0,05-0,15 mg/kg (0,15-0,3 senza premedicazione)	
Componente sedativo in anestesia combinata	*e.v.* Dosi intermittenti di 0,03-0,1 mg/kg o infusione continua di 0,03-0,1 mg/kg/h	*e.v.* Dosi inferiori a quelle consigliate per adulti < 60 anni	
Sedazione in terapia intensiva	*e.v.* Dose di carico: 0,03-0,3 mg/kg con incrementi di 1-2,5 mg Dose di mantenimento: 0,03-0,2 mg/kg/h		***e.v. in neonati < 32 settimane di età gestazionale*** 0,03 mg/kg/h ***e.v. in neonati > 32 settimane e bambini fino a 6 mesi*** 0,06 mg/kg/h ***e.v. in pazienti di età > 6 mesi*** Dose di carico: 0,05-0,2 mg/kg Dose di mantenimento: 0,06-0,12 mg/kg/h

Posologia sottocutanea Proposta Adulti

- *Agitazione:* somministrare 5 mg in bolo di midazolam per via sottocutanea con successive dosi aggiuntive di 1 mg in bolo a distanza di 20 minuti, fino al controllo del sintomo. Ove ritenuto necessario, al fine di garantire un controllo prolungato del sintomo, somministrare 20-150 mg nelle 24 ore in infusione continua per via sottocutanea.
- *Convulsioni:* somministrare 20-40 mg nelle 24 ore in infusione continua per via sottocutanea.
- *Sedazione in corso di pratiche diagnostiche, terapeutiche e assistenziali:* somministrare una dose di midazolam in bolo di 0,05 mg/kg da ripetere in caso di necessità per via sottocutanea a distanza di 10-20 minuti, fino all'effetto desiderato.

- *Sedazione palliativa:* dose di midazolam di 10-120 mg nelle 24 ore, in infusione sottocutanea continua. Dosaggi più elevati sono in genere richiesti e andranno quindi considerati nelle seguenti condizioni:
  - pazienti giovani;
  - pregresso uso di benzodiazepine;
  - sedazione prolungata (per tolleranza).

Bibliografia aggiuntiva relativa al dosaggio del midazolam. Parole chiave: "MIDAZOLAM AND PALLIATIVE CARE DOSAGE"

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SEDAZIONE PALLIATIVA

Per sedazione palliativa si intende la riduzione intenzionale della vigilanza con mezzi farmacologici, fino alla perdita di coscienza, allo scopo di ridurre o abolire la percezione di un sintomo, altrimenti intollerabile per il paziente, nonostante siano stati messi in opera i mezzi più adeguati per il controllo di un sintomo che risulta, quindi, refrattario.

Tale atto è ragionevolmente inteso che debba essere intrapreso nella fase avanzata ed evolutiva di un paziente affetto da malattia inguaribile.

DEFINIZIONE DI "SINTOMO REFRATTARIO" PER L'AVVIO DI UNA SEDAZIONE PALLIATIVA

Sintomo che angoscia il paziente e che non è adeguatamente controllabile nonostante sia stato fatto ogni sforzo teso ad identificare una terapia che sia efficace e tollerabile da parte del paziente e che non comprometta il livello di coscienza del malato.

GESTIONE DEL SINTOMO DELIRIO da**:** PALLIATIVE CARE IN THE DEVELOPING WORLD PRINCIPLES AND PRACTICE - Eduardo Burera, MD; Liliana De Lima, MHA; Roberto Wenk, MD and William Farr, MD, 2010	
Step 1: Valutare il Paziente	• Mantenere un alto grado di sospetto e allerta. Usare strumenti di valutazione validati come il *MMSE, Clock-making, o la Memorial Delirium Assessment Scale.* Questi strumenti dovrebbero essere usati solo quando non vi sono segni evidenti di delirio e al solo fine di una diagnosi precoce.

	• Raccogliere informazioni dal paziente circa la tipologia di allucinazione (più spesso tattile che visiva) e ideazione non aderente alla realtà. I pazienti non forniscono di frequente e in modo volontario, informazioni circa questi sintomi. • Ricercare segni clinici di sepsi, tossicità da farmaci (anche oppiacei), disidratazione, alterazioni metaboliche, o alter cause organiche di delirio. • Prescrivere esami specifici, ad esempio controllo di emocromo, elettroliti, calcemia (con albuminemia), funzionalità renale Rx Torace, SpO_2 e tutti gli altri esami ritenuti indicati.
Step 2: Trattare le cause sottostanti	• **Tossicità da oppiacei**: ruotare gli oppiacei. • **Sepsi:** iniziare un trattamento antibiotico appropriato dopo discussione con il paziente e i familiari. • **Farmaci**: sospendere tutti i farmaci che potenzialmente possono scatenare o peggiorare il delirio come: antidepressivi triciclici, benzodiazepine, alcuni antiemetici, antibiotici e cimetidina. • **Disidratazione**: se non è disponibile una via EV, iniziare un ipodermoclisi, soluzione salina fisiologica a 60 - 100 ml/h, o in alternativa somministrare boli di 500 ml tre volte al giorno. • **Ipercalcemia**: tratta con bifosfonati. • **Ipossia**: se possibile, trattare le cause sottostanti e somministrare ossigeno. • **Tumori o metastasi cerebrali**: valutare steroidi ad alte dosi.
Step 3: Trattare i sintomi del delirio	• **Agitazione/Allucinazione**: Per trattare l'agitazione, iniziare aloperidolo 2 mg solo per uso orale e sottocute ogni 6 h e 2 mg ogni 1 h po/sc secondo le necessità del paziente. Per il controllo rapido di agitazione severa, può rendersi necessario incrementare i dosaggi sino a 2 mg ogni 15 - 30 min sc/per os o secondo le necessità del paziente nella prima ora e ogni ora secondo le necessità del paziente, a seguire. È molto importante controllare velocemente il sintomo per prevenire il distress del paziente, dei familiari, del caregiver e dell'equipe. Appena il sintomo è controllato, ridurre il dosaggio alla minima dose efficace, il prima possibile. Quando si debba avviare l'infusione di Aloperidolo o di altri farmaci antipsicotici (come la clorpromazina o la perfenazina), si raccomanda la consulenza di un medico palliativista o di uno psichiatra. In rare occasioni è richiesto un approccio aggressivo; in questi casi si consiglia l'infusione di midazolam 1 mg/h sc, aggiustando il dosaggio in base alla risposta clinica.

Step 4: Fornisci supporto ai familiari, al caregiver e alla equipe	La confusione mentale e l'agitazione sono espressione di un disturbo neurologico, ma non sono necessariamente legati a discomfort per il paziente. La disinibizione è una delle componenti principali del delirio e può essere causa di due fenomeni stressanti: • Espressioni drammatiche intercorrenti, caratterizzate da smorfie e lamenti: i familiari potrebbero interpretare questi fenomeni come un aggravamento della situazione clinica piuttosto che semplicemente un aumento delle manifestazioni espressive del paziente. Ciò potrebbe indurre un aumentato e inappropriato ricorso a farmaci oppiacei o sedativi. • Richieste irragionevoli ai familiari e all'equipe (ad esempio: "Voglio andare a casa ora."). Se queste richieste non vengono prontamente esaudite, il paziente potrebbe divenire aggressivo. Deve essere spiegato in modo approfondito ai familiari che la richiesta è formulata e dettata dal delirio.

Quando si avvia una sedazione palliativa, la scelta accurata dei farmaci e delle modalità di somministrazione è un aspetto fondamentale e deve essere strettamente integrata con altri fattori come il setting di esecuzione, l'esperienza dell'equipe, fattori biologici, via di somministrazione e molti altri. Per quanto riguarda la sedazione palliativa si rimanda alle **Raccomandazioni della Società Italiana di Cure Palliative (SICP) del 2007**. Il monitoraggio deve essere garantito e generalmente si utilizza la scala di Rudkin sotto riportata.

Grado di sedazione: scala di Rudkin	
1	Paziente sveglio e orientato
2	Sonnolente ma risvegliabile
3	Occhi chiusi ma risvegliabile alla chiamata
4	Occhi chiusi ma risvegliabile a stimolo tattile (non doloroso)
5	Occhi chiusi non rispondente a uno stimolo tattile

Non vi è consenso univoco sul grado iniziale di sedazione da attuare, anche se vi sono indicazioni in letteratura con cui si può concordare: iniziare con una sedazione superficiale e passare a una sedazione profonda nei casi in cui la sedazione superficiale non raggiunga lo scopo della stessa o per richiesta esplicita del paziente, ad esclusione di quelle situazioni cliniche acute in cui il rischio di morte sia imminente.

La scelta dei farmaci da utilizzare dipende in notevole misura dall'esperienza, conoscenza

e pratica dell'equipe. Non vi è consenso univoco sulla scelta dei farmaci da adottare, anche se il midazolam è la benzodiazepina più utilizzata in letteratura, dalla quale si evince chiaramente come la ST/SP debba essere attuata con sedativi e non con aloperidolo od oppioidi.

Ad oggi la letteratura considera il midazolam il farmaco di prima scelta, come riportato nella tabella sottostante.

PAZIENTE	FARMACO	COMPATIBILITÀ E AVVERTENZE	DOSE INDUZIONE (usuale)	DOSE MANTENIMENTO (usuale)	VIA DI SOMM.
ADULTO	1° scelta: MIDAZOLAM (concentrazione: 1 mg in 1 ml di sol glucosata o salina)	oppioidi, soluzione fisiologica, glucosata	BOLO: 2,5-5 mg (0,05-0,07mg/Kg) Oppure IN CONTINUO: 0,2-1 mg/h (più dosi supplementari di 1,25-2,5 mg)	10-120 mg/die (0,03-0,05 mg/Kg/h op. 0,5-5 mg/h)	s.c.-e.v.- (rettale-i.m.)

ABSTRACT RICHIESTA 1:

1. Franken LG

Midazolam is the drug of choice for palliative sedation and is titrated to achieve the desired level of sedation. A previous pharmacokinetic (PK) study showed that variability between patients could be partly explained by renal function and inflammatory status. The goal of this study was to combine this PK information with pharmacodynamic (PD) data, to evaluate the variability in response to midazolam and to find clinically relevant covariates that may predict PD response. A population pharmacodynamic analysis using nonlinear mixed effect models was performed with data from 43 terminally ill patients. PK profiles were predicted by a previously described PK model and depth of sedation was measured using the Ramsay sedation score. Patient and disease characteristics were evaluated as possible covariates. The final model was evaluated using a visual predictive check (VPC). The effect of midazolam on the sedation level was best described by a differential odds model including a baseline probability, Emax model and inter individual variability (IIV) on the overall effect. The EC50 value was 68.7 ug/L for a Ramsay score of 3-5 and 117.1 ug/L for a Ramsay score of 6. Co-medication with haloperidol was the only significant covariate. The VPC of the final model showed good model predictability. That describe the clinical response to midazolam. As expected there was large variability in response to midazolam. The use of haloperidol was associated with a lower probability of sedation. This may be a result of confounding by indication as haloperidol was used to treat delirium, and deliria has been linked to a more difficult sedation procedure.

2. Franken LG

A variety of medications are used for symptom control in palliative care, such as morphine, midazolam and haloperidol. The pharmacokinetics of these drugs may be altered in these patients as a result of physiological changes that occur at the end stage of life. This review gives an overview of how the pharmacokinetics in terminally ill patients may differ from the average population and discusses the effect of terminal illness on each of the four pharmacokinetic processes absorption, distribution, metabolism, and elimination. Specific considerations are also given for three commonly prescribed drugs in palliative care: morphine, midazolam and haloperidol). The pharmacokinetics of drugs in terminally ill patients can be complex and limited evidence exists on guided drug use in this population. To improve the quality of life of these patients, more knowledge and more pharmacokinetic/pharmacodynamics studies in terminally ill patients are needed to develop individualised dosing guidelines. Until then knowledge of pharmacokinetics and the physiological changes that occur in the final days of life can provide a base for dosing adjustments that will improve the quality of life of terminally ill patients. As the interaction of drugs with the physiology of dying is complex, pharmacological treatment is probably best assessed in a multi-disciplinary setting and the advice of a pharmacist, or clinical pharmacologist, is highly recommended.

3. Bobb B

Palliative sedation has become a standard practice to treat refractory symptoms at end-of-life. Dyspnea and delirium are the two most commonly treated symptoms. The medications used in palliative sedation are usually benzodiazepines, barbiturates, antipsychotics, and/or anesthetics. Some ethical considerations remain, especially surrounding the use of palliative sedation in psychological distress and existential suffering.

4. Lindqvist O

The majority of dying patients do not have access to necessary drugs to alleviate their most common symptoms, despite evidence of drug efficacy. Our aim was to explore the degree of consensus about appropriate pharmacological treatment for common symptoms in the last days of life for patients with cancer, among physicians working in specialist palliative care. Within OPCARE9, a European Union seventh framework project aiming to optimize end-of-life cancer care, we conducted a Delphi survey among 135 palliative care clinicians in nine countries. Physicians were initially asked about first and second choice of drugs to alleviate anxiety, dyspnea, nausea and vomiting, pain, respiratory tract secretions (RTS), as well as terminal restlessness. Based on a list of 35 drugs mentioned at least twice in the first round (n=93), a second Delphi round was performed to determine ≤ 5 essential drugs for symptom alleviation in the last 48 hours of life that should be available even outside specialist palliative care. There was ≥ 80% consensus among the participants (n=90) regarding morphine, midazolam, and haloperidol as essential drugs. For RTS, there was consensus about use of an antimuscarinic drug, with 9%-27% of the physicians each choosing one of four different drugs. Based on this consensus opinion and other literature, we suggest four drugs that should be made available in all settings caring for dying patients

with cancer, to decrease the gap between knowledge and practice: morphine (i.e., an opioid), midazolam (a benzodiazepine), haloperidol (a neuroleptic), and an antimuscarinic.

5. Lawlor PG

Delirium is a frequent neurocognitive complication in patients with cancer, particularly in patients with advanced-stage disease (in whom a combination of factors might trigger an episode) and in patients with a high degree of predisposing vulnerability, such as the elderly or patients with dementia. The communicative impediments associated with delirium generate distress for the patient and their family, and substantive challenges for health-care practitioners, who might have to contend with agitation, and difficulty in assessing pain and other symptoms. Validated assessment tools exist for screening, diagnosing and monitoring the severity of delirium in cancer care. The level of investigative and therapeutic intervention in a delirium episode is determined by the patient's estimated prognosis and the agreed goals of care. Although delirium is ominously associated with the terminal phase of life, part or complete reversal can be possible depending on the nature of the precipitating factors, and on whether investigation and treatment of these factors is consistent with the established goals of care. Pharmacological treatment for symptom control is indicated for most patients with delirium, and antipsychotics are the drugs of choice, but some patients with refractory and nonreversible delirium can require continuous deep sedation with agents such as midazolam.

6. Chakraborti D

The objective of this review is to summarize the available data on the use of melatonin and melatonin agonist for the prevention and management of delirium in the elderly patients from randomized controlled trials (RCTs). A systematic search of 5 major databases PubMed, MEDLINE, PsychINFO, Embase, and Cochrane Library was conducted. This search yielded a total of 2 RCTs for melatonin. One study compared melatonin to midazolam, clonidine, and control groups for the prevention and management of delirium in individuals who were pre- and posthip post-hip arthroplasty. The other study compared melatonin to placebo for the prevention of delirium in older adults admitted to an inpatient internal medicine service. Data from these 2 studies indicate that melatonin may have some benefit in the prevention and management of delirium in older adults. However, there is no evidence that melatonin reduces the severity of delirium or has any effect on behaviors or functions in these individuals. Melatonin was well tolerated in these 2 studies. The search for a melatonin agonist for delirium in the elderly patients yielded 1 study of ramelteon. In this study, ramelteon was found to be beneficial in preventing delirium in medically ill individuals when compared to placebo. Ramelteon was well tolerated in this study.

7. Gonçalves F

Agitation is a distressing and dangerous behavior for all involved. To study a protocol effectiveness and safety. The time when the protocol was initiated and when

the agitation was controlled, the number of doses needed and the complications observed were recorded. One hundred and thirty-five inpatients of a palliative care service were included. The most frequent diagnosis was head and neck cancer, 37 (27%). The protocol was used 584 times, from 1 to 31 times on each patient, median of 3 times. Five hundred and thirty-four (91%) agitation episodes were controlled with only the first dose of the protocol, without significant complications. From those results, it can be said that this protocol is effective and safe.

8. Lawlor PG

Delirium is a frequent neurocognitive complication in patients with cancer, particularly in patients with advanced-stage disease (in whom a combination of factors might trigger an episode) and in patients with a high degree of predisposing vulnerability, such as the elderly or patients with dementia. The communicative impediments associated with delirium generate distress for the patient and their family, and substantive challenges for health-care practitioners, who might have to contend with agitation, and difficulty in assessing pain and other symptoms. Validated assessment tools exist for screening, diagnosing and monitoring the severity of delirium in cancer care. The level of investigative and therapeutic intervention in a delirium episode is determined by the patient's estimated prognosis and the agreed goals of care. Although delirium is ominously associated with the terminal phase of life, part or complete reversal can be possible depending on the nature of the precipitating factors, and on whether investigation and treatment of these factors is consistent with the established goals of care. Pharmacological treatment for symptom control is indicated for most patients with delirium, and antipsychotics are the drugs of choice, but some patients with refractory and nonreversible delirium can require continuous deep sedation with agents such as midazolam.

ABSTRACT RICHIESTA 2:

1. Leon Ruiz M

Very little has been written on seizure management in palliative care (PC). Given this situation, and considering the forthcoming setting up of the Palliative Care Unit at our neurorehabilitation centre, the Clínica San Vicente, we decided to establish a series of guidelines on the use of antiepileptic drugs (AEDs) for handling seizures in PC. We conducted a literature search in PubMed to identify articles, recent manuals, and clinical practice guidelines on seizuremanagement in PC published by the most relevant scientific societies. Clinical practice guidelines are essential to identify patients eligible for PC, manage seizures adequately, and avoid unnecessary distress to these patients and their families. Given the profile of these patients, we recommend choosing AEDs with a low interaction potential and which can be administered by the parenteral route, preferably intravenously. Diazepam and midazolam appear to be the most suitable AEDs during the acute phase whereas levetiracetam, valproic acid, and lacosamide are recommended for refractory cases and long-term treatment. These guidelines provide general recommendations that must be adapted to each particular clinical case. Nevertheless, we will require further well-designed randomised controlled clinical trials including large samples of patients eligible for PC to draft a consensus document

recommending adequate, rational, and effective use of AEDs, based on a high level of evidence, in this highly complex area of medical care.

2. Harris N

Controlling seizures in children approaching death can be difficult, and there is a limited evidence base to guide best practice. We compared current practice against the guidance for seizure management produced by the Association of Paediatric Palliative Medicine (APPM). Retrospective case note review of episodes of challenging seizure management in children receiving end-of-life care over a 10-year period (2006-2015) in the south-west region of England. We reviewed 19 admissions, in 18 individuals. Six (33%) had a malignancy, nine (50%) had a progressive neurodegenerative condition and three (17%) had a static neurological condition with associated epilepsy. Thirteen (72%) died in their local hospice, four (22%) at home, and one (6%) in hospital. Seventeen of 19 episodes involved the use of subcutaneous or intravenous midazolam infusion, for a mean of 11 days (range 3-27). There was a wide range of starting doses of midazolam, and 9/17 (53%) received final doses in excess of current dose recommendations. Six individuals received subcutaneous phenobarbital infusions, with four of these (67%) receiving final doses in excess of current dose recommendations. Plans for adjustments of infusion rates, maximal doses or alternative approaches should treatment fail were inconsistent or absent. In 16/18 (88%) cases seizures were successfully controlled prior to the day of the child's death. Staff found the experience of managing seizures at end of life challenging and stressful. Pharmacological approaches to seizure management in end-of-life care are variable, often exceeding APPM dose recommendations. Despite this, safe and effective seizure control was possible in all settings.

ABSTRACT RICHIESTA 3:

1. Gonçalves F

The teams included on the website of the Portuguese Association for Palliative Care were invited to participate. Data from all the patients sedated between April and June 2010 were recorded. Sedation was defined as the intentional administration of sedative drugs for symptom control, except insomnia, independently of the consciousness level reached. Of the 19 teams invited only 4 actually participated. During the study period, 181 patients were treated: 171 (94 %) were cancer patients and 10 non-cancer patients. Twenty-seven (16 %) patients were sedated: 13 intermittently, 11 continuously, and 3 intermittently at first then continuously. The rate of sedation varied substantially among the teams. Delirium was the most frequent reason for sedation. Midazolam was the drug used in most cases. In 21 cases of sedation, the decision was made unilaterally by the professionals; in 16 (76 %) of those, the situation was deemed to be emergent. From the patients on continuous sedation, 9 (64 %) patients maintained oxygen, 13 (93 %) hydration, and 6 (43 %) nutrition. Two patients who had undergone intermittent sedation were discharged home and one was transferred to another institution; the reason for sedation in the three cases was delirium. There is a substantial variation in the sedation rate among the teams. One of the most important aspects was the decision-making process which should be object of

reflection and discussion in the teams.

2. Kaneishi K

Insomnia is one of the most common complications affecting patients with advanced cancer. Severe insomnia has a highly negative impact on quality of life. Sleeplessness exacerbates pain, causing physical and mental discomfort (e.g., fatigue, daytime drowsiness, and day-night reversal). As with other symptoms, insomnia is distressing to patients, families, and caregivers. Furthermore, with the progression of disease, many patients with advanced cancer face difficulties taking oral medication, eventually requiring parenteral drug administration. The placement of an intravenous catheter is often uncomfortable and difficult for patients with advanced cancer. In such patients, single-dose subcutaneous administration is easier and less stressful as compared with intravenous administration. Benzodiazepines are commonly used hypnotic medications for inducing sleep in palliative care. Midazolam and flunitrazepam as injectable solutions can be used in Japan. Midazolam is a short-acting and flunitrazepam an intermediate-acting benzodiazepine. For the last eight years, we have successfully used midazolam and flunitrazepam for treating insomnia via single-dose subcutaneous administration. Single-dose administration is advantageous because it does not need specialized equipment, being simple and useful for patients and medical institutions, including patients receiving home care. However, to the best of our knowledge, single-dose subcutaneous administration of midazolam and flunitrazepam for treating insomnia has not been reported thus far.

3. Matsuo N

Although intravenous midazolam and flunitrazepam are frequently administered for primary insomnia in Japan, there is no empirical study on their efficacy and safety.
To compare the efficacy, safety, and cost-effectiveness of midazolam and flunitrazepam a multicenterretrospective audit study was performed on 104 and 59 patients receiving midazolam and flunitrazepam, respectively, from 18 certified palliative care units. Median administration periods were 6 days and 9 days for midazolam and flunitrazepam, respectively. The median initial and maximum doses were 10 mg per night and 18 mg per night for midazolam, and 2 mg per night and 2 mg per night for flunitrazepam, respectively. There were no significant differences in the efficacy (91% in the midazolam group versus 81% in the flunitrazepam group, $p = 0.084$), hangover effect (34% versus 19%, $p = 0.094$), delirium at night (12% versus 10%, $p = 1.0$) and delirium next morning (11% versus 15%, $p = 0.33$), treatment withdrawal (4.8% versus 1.7%, $p = 0.41$), and treatment-related death (0% versus 0%, $p = 1.0$). Flunitrazepam caused respiratory depression defined as physician or nurses records such as apnea, respiratory arrest, decreased respiratory rate, and respiratory depression significantly more frequently than midazolam (17% versus 3.8%, $p = 0.0073$). The maximum dose was more highly correlated with the administration period in the midazolam group than in the flunitrazepam group (rho = 0.52, versus rho = 0.39), and, for patients treated for 14 days or longer, the daily escalation dose ratio required for maintaining adequate sleep was significantly higher in the midazolam group than in the flunitrazepam group (11% versus 2.6%, $p = 0.015$). The costs of the initial and

maximum administration were significantly higher in the midazolam group than in the flunitrazepam group ($p < 0.001$). Intravenous midazolam and flunitrazepam appeared to be almost equal about efficacy and safety for primary insomnia, but flunitrazepam is less expensive and shows lower risk of tolerance development. A future prospective comparison study is necessary.

ABSTRACT RICHIESTA 4:

1. Schildmann EK

Palliative sedation therapy (PST) is increasingly used in patients at the end of life. However, consensus about medications and monitoring is lacking. To assess published PST guidelines with regard to quality and recommendations on drugs and monitoring. We searched CINAHL, the Cochrane Library, Embase, PsycINFO, PubMed, and references of included articles until July 2014. Search terms included "palliative sedation" or "sedation" and "guideline" or "policy" or "framework." Guideline selection was based on English or German publications that included a PST guideline. Two investigators independently assessed the quality of the guidelines according to the Appraisal of Guidelines for Research and Evaluation II instrument (AGREE II) and extracted information on drug selection and monitoring. Nine guidelines were eligible. Eight guidelines received high quality scores for the domain "scope and purpose" (median 69%, range 28-83%), whereas in the other domains the guidelines' quality differed considerably. The majority of guidelines suggest midazolam as drug of first choice. Recommendations on dosage and alternatives vary. The guidelines' recommendations regarding monitoring of PST show wide variation in the number and details of outcome parameters and methods of assessment. The published guidelines on PST vary considerably regarding their quality and content on drugs and monitoring. Given the need for clear guidance regarding PST in patients at the end of life, this comparative analysis may serve as a starting point for further improvement.

2. De Graeff A

Palliative sedation therapy (PST) is a controversial issue. There is a need for internationally accepted definitions and standards. A systematic review of the literature was performed by an international panel of 29 palliative care experts. Draft papers were written on various topics concerning PST. This paper is a summary of the individual papers, written after two meetings and extensive e-mail discussions. PST is defined as the use of specific sedative medications to relieve intolerable suffering from refractory symptoms by a reduction in patient consciousness, using appropriate drugs carefully titrated to the cessation of symptoms. The initial dose of sedatives should usually be small enough to maintain the patients' ability to communicate periodically. The team looking after the patient should have enough expertise and experience to judge the symptom as refractory. Advice from palliative care specialists is strongly recommended before initiating PST. In the case of continuous and deep PST, the disease should be irreversible and advanced, with death expected within hours to days. Midazolam should be considered first-line choice. The decision whether or not to withhold or withdraw hydration should be discussed separately. Hydration should be offered only if it is considered likely

that the benefit will outweigh the harm. PST is distinct from euthanasia because (1) it has the intent to provide symptom relief, (2) it is a proportionate intervention, and (3) the death of the patient is not a criterion for success. PST and its outcome should be carefully monitored and documented. When other treatments fail to relieve suffering in the imminently dying patient, PST is a valid palliative care option.

3. Simon ST

This is an updated version of the original Cochrane review published in Issue 1, 2010, on Benzodiazepines for the reliefof breathlessness in advanced malignant and non-malignant diseases in adults'. Breathlessness is one of the most common symptoms experienced in the advanced stages of malignant and non-malignant disease. Benzodiazepines are widely used for the relief of breathlessness in advances diseases and are regularly recommended in the literature. At the time of the previously published Cochrane review, there was no evidence for a beneficial effect of benzodiazepines for the relief of breathlessness in people with advanced cancer and chronic obstructive pulmonary disease (COPD). The primary objective of this review was to determine the efficacy of benzodiazepines for the relief breathlessness in people with advanced disease. Secondary objectives were to determine the efficacy of different benzodiazepines, different doses of benzodiazepines, different routes of application, adverse effects of benzodiazepines, and the efficacy in different disease groups. This is an update of a review published in 2010. We searched 14 electronic databases up to September 2009 for the original review. We checked the reference lists of all relevant studies, key textbooks, reviews, and websites. For the update, we searched CENTRAL, MEDLINE, and EMBASE and registers of clinical trials for further ongoing or unpublished studies, up to August 2016. We contacted study investigators and experts in the field of palliative care asking for further studies, unpublished data, or study details when necessary. We included randomised controlled trials (RCTs) and controlled clinical trials (CCTs) assessing the effect of benzodiazepines compared with placebo or active control in relieving breathlessness in people with advanced stages of cancer, chronic obstructive pulmonary disease (COPD), chronic heart failure (CHF), motor neurone disease (MND), and idiopathic pulmonary fibrosis (IPF). Two review authors independently assessed identified titles and abstracts. Three review authors independently performed assessment of all potentially relevant studies (full text), data extraction, and assessment of methodological quality. We carried out meta-analysis where appropriate. Overall, we identified eight studies for inclusion: seven in the previous review and an additional study for this update. We also identified two studies awaiting classification in this update. The studies were small (a maximum number of 101 participants) and comprised data from a total of 214 participants with advanced cancer or COPD, which we analysed. There was only one study of low risk of bias. Most of the studies had an unclear risk of bias due to lack of information on random sequence generation, concealment, and attrition. Analysis of all studies did not show a beneficial effect of benzodiazepines for the relief of breathlessness (the primary outcome) in people with advanced cancer and COPD (8 studies, 214 participants) compared to placebo, midazolam, morphine, or promethazine. Furthermore, we observed no statistically significant effect in the prevention of episodic breathlessness (breakthrough dyspnoea) in people with cancer (after 48 hours: risk ratio of 0.76 (95% CI 0.53 to 1.09; 2 studies, 108 participants)) compared to morphine. Sensitivity analyses demonstrated no statistically significant differences regarding type of benzodiazepine, dose, route and frequency of delivery, duration of treatment, or type of

control. Benzodiazepines caused statistically significantly more adverse events, particularly drowsiness and somnolence, when compared to placebo (risk difference 0.74 (95% CI 0.37, 1.11); 3 studies, 38 participants). In contrast, two studies reported that morphine caused more adverse events than midazolam (RD -0.18 (95% CI -0.31, -0.04); 194 participants). Since the last version of this review, we have identified one new study for inclusion, but the conclusions remain unchanged. There is no evidence for or against benzodiazepines for the relief of breathlessness in people with advanced cancer and COPD. Benzodiazepines caused more drowsiness as an adverse effect compared to placebo, but less compared to morphine. Benzodiazepines may be considered as a second- or third-line treatment, when opioids and non-pharmacological measures have failed to control breathlessness. There is a need for well-conducted and adequately powered studies.

4. Morita T

Although palliative sedation therapy is often required in terminally ill cancer patients to achieve acceptable symptom relief, empirical data supporting the ethical validity of this approach are lacking. The primary aim of this study was to systematically investigate whether empirical evidence supports the ethical validity of sedation. This was a multicenter, prospective, observational study, which was conducted by 21 specialized palliative care units in Japan. One-hundred two consecutive adult cancer patients who received continuous deep sedation were enrolled. Continuous deep sedation was defined as the continuous use of sedative medications to relieve intolerable and refractory distress by achieving almost or complete unconsciousness until death. Prior to the study, we conceptualized the ethicalvalidity of sedation from the viewpoints of physicians' intent, proportionality, and autonomy. Sedation was performed mainly with midazolam and phenobarbital. The initial doses of midazolam and phenobarbital were 1.5 mg/hour and 20 mg/hour, respectively. Main administration routes were continuous subcutaneous infusion and continuous intravenous infusion, and no rapid intravenous injection was reported. Of 59 patients who received artificial hydration or could intake adequate fluids/foods orally before sedation, 63% received artificial hydration therapy after sedation, and in the remaining patients, artificial hydration was withheld or withdrawn due to fluid retention symptoms and/or patient wishes. Of 66 patients who were able to verbally express themselves, 95% explicitly stated that symptoms were intolerable. The etiologies of the symptoms requiring sedation were primarily related to the progression of the underlying malignancy, such as cancer cachexia and organ failure, and standard palliative treatments had failed: steroids in 68% of patients with fatigue, opioids in 95% of patients with dyspnea, antisecretion medications in 75% of patients with bronchial secretion, antipsychotic medications in 74% of patients with delirium, and opioids in all patients with pain. On the basis of the Palliative Prognostic Index, 94% of the patients were predicted to die within 3 weeks. Before sedation, 67% of the patients expressed explicit wishes for sedation. In the remaining 34 patients, previous wishes for sedation were noted in 4 patients, and in the other 30 patients, the families were involved in the decision-making process. The chief reason for patient non-involvement in the decision making was cognitive impairment. These data indicate that palliative sedation therapy performed in specialized palliative care units in Japan generally followed the principles of double effect, proportionality, and autonomy.

5. Bartz L

Especially in palliative care, safe and manageable administration of medication is essential. Subcutaneous drug administration is a possible alternative, when oral intake is hampered. However, evidence for this method is rare. This observational study assessed the clinical practice of subcutaneous drug administration, focusing on the evaluation of local reactions or complications to further develop recommendations. Over 14 months, patients in a specialized inpatient palliative care unit treated by the subcutaneous route were invited to participate in this clinical study. All subcutaneous medications including dosage and volume of injection, type of needles, and injection site were documented. The injection sites were systematically assessed including the subjective perceptions of patients for analysis of patient tolerability and acceptability. T-tests and Chi-squared tests of these variables were performed to calculate group differences between needles with vs. without complications ($P < 0.05$). In 120 patients, 3957 applications were administered via 243 needles. The needles were placed in thighs (38.7%) and upper arms (28.8%). Most frequently used medications were hydromorphone (59.0%), haloperidol (12.3%), and midazolam (8.3%). Complications were diagnosed most often on the third or fourth day of the needle in situ and occurred significantly more often in (fully) active patients and patients transferred or discharged at the end of treatment. The mean time of needle in situ was significantly lower (4.1 vs. 5.0 days) in complication cases than in noncomplication cases (t-test: $P = 0.027$). The results of this study acknowledge the clinical practice of subcutaneous administration of medication as a very flexible, broadly feasible, rather safe, and nonburdensome method. Nevertheless, this practice is not free from complications, needs appropriate nursing care, and requires standardized policies and procedures.

6. Bleasel MD

We have investigated the steady-state plasma concentrations of midazolam during continuous subcutaneous administration in palliativecare. Using a sensitive gas chromatography with electron capture detector assay, plasma concentrations of midazolam were measured in 11 patients (median age 68 years; range 47-82 years; six females) receiving the drug by continuous subcutaneous infusion (median rate 20 mg/day; range 10-60 mg/day). While not significant, the infusion rate tended to decrease with increasing age of the patient (Spearman's $p = -0.51$; $p = 0.11$). The steady-state plasma concentration range was 10-147 ng/ml, with a median of 30 ng/ml. Infusion rates and plasma concentrations of midazolam were correlated (Spearman's $p = 0.71$; $p < 0.05$). No other significant relationships were found between plasma concentrations and the variables of age, sex and liver function.

7. Levy MH

There is a continuum of the goals of comfort and function in palliative care that begins with comfort and function being equal priorities and sedation being unacceptable. As disease progresses, the goals and preferences of the patient turn to coping with the loss of function caused by the disease and acceptance of unintentional sedation from the disease, its therapies, or symptom relief interventions. As patients approach the end of life,

they may need intentional sedation for the relief of refractory symptoms. Such sedation can be divided into three categories: routine, infrequent, and extraordinary with respect to the frequency, difficulty, and risks involved with the drugs and routes of administration required to induce and maintain a level of sedation that relieves the patient's physical and existential symptoms. Extraordinary sedation with continuous infusions of midazolam, thiopental, and propofol can relieve refractory symptoms in most patients in their final days of life. Palliative care clinicians should become comfortable with the ethical justification and technical expertise needed to provide this essential, extraordinary care to the small but deserving number of patients in whom routine and infrequent sedation does not adequately relieve their suffering.

RCT DISPONIBILI:

1. Pecking M

Midazolam is given intravenously for induction of anaesthesia and conscious sedation and by subcutaneous infusion in patients in palliative care units. The objective of the present study was to determine the absolute bioavailability of subcutaneous midazolam and its pharmacokinetics in young, healthy, male volunteers.
METHODS: Eighteen volunteers were given single doses of 0.1 mg kg-1 midazolam i.v. and s.c. after a wash-out period of 7-15 days in an open-label, randomized, cross-over study. Blood samples were collected up to 12 h post-infusion. Plasma concentrations of midazolam and of its two metabolites, 1'-OHM and 4-OHM, were assessed using an h.p.l.c.-MS method (LOQ 0.5 ng ml-1 for each analyte). Vital signs, cardiac parameters and oximetry were monitored. Local tolerance was determined and adverse events were also monitored.RESULTS: After s.c. infusion t(max) and C(max) were 0.51 +/- 0.18 h and 127.8 +/- 29.3 ng ml-1 (mean +/- s.d.), respectively. No statistically significant difference was detected in AUC(0, infinity) after i.v. and s.c. administration.

The mean (+/-s.d.) absolute bioavailability of subcutaneous midazolam was 0.96 (+/- 0.14) (CI 0.84, 1.03). Mean (+/- s.d.) t1/2 was similar after s.c. (3.2 (+/- 1.0) h) and i.v. infusion (2.9 (+/- 0.7) h), although a statistically significant difference was reached ($P < 0.05$). Mean CL and V of i.v. midazolamwere 4.4 +/- 1.0 ml min-1 kg-1 and 1.1 +/- 0.2 l kg-1 (mean +/- s.d.), respectively. Plasma concentrations of 1'-OHM were higher than those of 4-OHM. Few mild and transient adverse events were noted and there were no clinically significant effects on EEG, blood pressure and laboratory parameters. CONCLUSIONS: This study has shown that subcutaneous midazolam has excellent bioavailability and that administration of midazolamby this route could be preferable when the intravenous route is inappropriate.

ABSTRACT RICHIESTA 5:

1. Mercadante S

Information about the attitudes towards palliative sedation (PS) at home is limited. The aim of this survey was to assess the attitude of palliative care physicians in Italy regarding PS at home. A questionnaire was submitted to a sample of palliative care physicians, asking

information about their activity and attitudestowards PS at home. This is a survey of home care physicians in Italy who were involved in end-of-life care decisions at home. One hundred and fifty participants responded.

A large heterogeneity of home care organizations that generate some problems was found. Indications, intention and monitoring of PS seem to be appropriate, although some cultural and logistic conditions were limiting the use of PS.
Specialized home care physicians are almost involved to start PS at home. Midazolam was seldom available at home and opioids were more frequently used. These data should prompt health care agencies to make a minimal set of drugs easily available for home care. Further research is necessary to compare attitudes in countries with different sociocultural profiles.

2. Calvo-Espinos C

Palliative sedation is a common treatment in palliative care. The home is a difficult environment for research, and there are few studies about sedation at home. Our aim was to analyze this practice in a home setting. We conducted a retrospective cross-sectional descriptive study in a home cohort during 2011. The inclusion criteria were as follows: 18 years or older and enrolled in the Palliative Home Care Program (PHCP) with advanced cancer. The variables employed were: sex, age, primary tumor location, and place of death. We also registered indication, type, drug and dose, awareness of diagnosis and prognosis, consent, survival, presence or absence of rales, painful mouth, and ulcers in patients sedated at home. We also collected the opinions of family members and professionals about the suffering of sedated patients. A total of 446 patients (56% at home) of the 617 admitted to the PHCP between January and December of 2011 passed away. The typical patient in our population was a 70-year-old man with a lung tumor. Some 35 (14%) home patients required sedation, compared to 93 (49%) at the hospital. The most frequent indication was delirium (70%), with midazolam the most common drug (mean dose, 40 mg). Survival was around three days. Rales were frequent (57%) as well as awareness of diagnosis and prognosis (77 and 71%, respectively). Perception of suffering after sedation was rare among relatives (17%) and professionals (8%). In most cases, the decision was made jointly by professionals and family members. Our study confirmed the role of palliative sedation as an appropriate therapeutic tool in the homeenvironment.

3. Daniel S

Many patients approaching the end of their life express the preference to die at home,[1] although unfortunately the majority of people will still die in hospital.[2] For patients approaching the end of their life, it was noted anecdotally that often those who have expressed a preference to go home from hospital for end of life care may have their discharge delayed due to problems in the prescribing of common medications used to alleviate distressing symptoms at the end of life. An initial audit at Conquest Hospital showed an 89% error rate in these prescriptions, mostly related to prescribing controlled drugs such as morphine and midazolam. A single standardised dispensing chart for commonly prescribed medications at the end of life, in the form of both

"Just in Case" medications and syringe driver medications, was created which addressed this problem by having the medications pre-written so as to meet all legal requirements for controlled drugs. The prescriber is able to choose and fill out an appropriate drug and dose by using flow-chart information overleaf and then sign the prescription to allow it to be dispensed. After an initial two month pilot period, a re-audit showed a significant fall in error rate down to 11%, as well as an improvement in turnaround time in dispensing the medications.

4. Mercadante S

The aim of this study was to assess a protocol for palliative sedation (PS) performed at home. A total of 219 patients were prospectively assessed to evaluate a PS protocol in patients with advanced cancer followed at home by two home care programs with different territorial facilities. The protocol was based on stepwise administration of midazolam. A total of 176 of the patients died at home, and PS was performed in 24 of these patients (13.6%). Younger patients received the procedure more frequently than older patients (P=0.012). The principal reasons to start PS were agitated delirium (n=20) and dyspnea (n=4). Mean duration of PS was 42.2±30.4 hours, and the mean doses of midazolam were 23-58 mg/day. Both the home careteam and the patients' relatives expressed optimal or good levels of satisfaction with the procedure in all but one case, respectively. This protocol for PS was feasible and effective in minimizing distress for a subgroup of patients who died at home. The characteristics of patients who may be effectively sedated at home should be better explored in future studies.

5. Alonso-Babarro A

Using a decision-making and treatment checklist developed to facilitate the at-home palliative sedation process, we assessed the incidence and efficacy of palliative sedation for end-of-life cancer patients with intractable symptoms who died at home. We retrospectively reviewed the medical records of 370 patients who were followed by a palliative home care team. Twenty-nine of 245 patients (12%) who died at home had received palliative sedation. The mean age of the patients who received palliative was 58 +/- 17 years, and the mean age of the patients who did not receive palliative sedation was 69 +/- 15 years (p = 0.002). No other differences were detected between patients who did or did not receive palliative sedation. The most common indications for palliativesedation were delirium (62%) and dyspnea (14%). Twenty-seven patients (93%) received midazolam for palliative sedation (final mean dose of 74 mg), and two (7%) received levomepromazine (final mean dose of 125 mg). The mean time between palliative sedationinitiation and time of death was 2.6 days. In 13 of the cases (45%), the palliative sedation decision was made with the patient and his or her family members, and in another 13 patients (45%), the palliative sedation decision was made only with the patient's family members. We concluded that palliative sedation may be used safely and efficaciously to treat dying cancer patients with refractory symptoms at home.

4.7. MORFINA solfato e MORFINA cloridrato

USO *OFF-LABEL* CHE SI VUOLE AUTORIZZARE:

1. Somministrazione per trattamento della **dispnea incontrollata che non risponde alla terapia della patologia di base nel paziente in fase avanzata di malattia.**

RAZIONALE DELLA RICHIESTA:

La dispnea è una sensazione soggettiva, frequentemente descritta dal paziente come fatica a respirare, fame d'aria, difficoltà a respirare, soffocamento. È un sintomo comune nei pazienti in fase terminale, indipendentemente dalla malattia iniziale, con grosse implicazioni sulla qualità di vita. L'impatto della dispnea incontrollata si riflette sulla famiglia e/o caregiver e naturalmente sull'equipe di cura. È un sintomo di "difficile trattamento" e può porre la famiglia, il paziente e l'equipe ad affrontare "decisioni difficili" (ventilazione assistita, cambio di setting assistenziale). Nel controllo del sintomo presenta un effetto positivo sul paziente, famiglia ed equipe. L'utilizzo di oppioidi è supportato da evidenze di livello 1 nell'efficacia nel ridurre del 20% la dispnea refrattaria in tutti i tipi di eziologia di dispnea (cardiaca, BPCO e tumorale) (J Pain Symptom Manage. 2007 Apr;33(4):473-81.Symptomatic therapy of dyspnea with strong opioids and its effect on ventilation in palliative care patients. - Clemens KE1, Klaschik E.; Wien Med Wochenschr. 2009 Dec;159(23-24):577-82. doi: 10.1007/s10354-009-0726-0. Opioids for symptomatic therapy of dyspnoea in patients with advanced chronic heart failure--is there evidence? Hochgerner M1, Fruhwald FM, Strohscheer I.).

Un precoce utilizzo di oppioidi migliora la qualità di vita e migliora la tolleranza agli effetti collaterali e/o depressione respiratoria (Dudgeon D 2001).

SITUAZIONE ATTUALE APPROVATA:

Trattamento del dolore da moderato a grave e/o resistente agli altri antidolorifici, in particolare dolore associato a neoplasie, a infarto miocardico e dopo gli interventi chirurgici. Edema polmonare acuto. La morfina, inoltre, è indicata in anestesia generale e loco-regionale e nella parto-analgesia epidurale.

RICERCA BIBLIOGRAFICA RICHIESTA 1:

Parole chiave: Opioids, dyspnea, palliation of breathlessness

Lavori evidenziati:

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2. Clemens KE et al. Symptomatic Therapy of Dyspnea with Strong Opioids and Its Effect on Ventilation in Palliative Care Patients. *J Pain Symptom Manage 2007;* 33:473-481.

3. Gomutbutra P et al. Management of Moderate-to-Severe Dyspnea in Hospitalized Patients Receiving Palliative Care. *J Pain Symptom Manage 2013;* 45:885-891.
4. Jennings AL et al. Opioids for the palliation of breathlessness in advanced disease and terminal illness. *Cochrane Database Syst Rev 2012;* 7:CD002066
5. Burke AL. *Palliative care: an update on "terminal restlessness".*Med J Aust. 1997 Jan 6;166(1):39-42
6. Documento intersocietario AIPO-SICP “Cure Palliative e trattamento della dispnea refrattaria nell’insufficienza respiratoria cronica” 5/2015
7. Strieder M[1], Pecherstorfer M[1], Kreye G[2].: Symptomatic treatment of dyspnea in advanced cancer patients : A narrative review of the current literature. Wien Med Wochenschr. 2017 Sep 18. doi: 10.1007/s10354-017-0600-4. [Epub ahead of print]
8. M. Kloke1 & N. Cherny2, on behalf of the ESMO Guidelines Committee*: Treatment of dyspnoea in advanced cancer patients: ESMO Clinical Practice Guidelines†Annals of Oncology 26 (Supplement 5): v169–v173, 2015

RCT DISPONIBILI:

No

ABSTRACT RICHIESTA 1:

1. Ben-Aharon I.

BACKGROUND. Dyspnea is commonly encountered by many cancer patients in the terminal stage of their disease and it severely hampers their quality of life. We aimed to evaluate the role of interventions to alleviate dyspnea. METHODS: Systematic review and meta-analysis of randomized controlled trials assessing all interventions for dyspnea palliation in cancer patients, and searched the Cochrane Library, MEDLINE, conference proceedings, and references. RESULTS: Our search yielded 18 trials. Eight studies evaluated opioids in any route of administration, seven studies evaluated the use of oxygen, two studies assessed the role of benzodiazepines and two studies evaluated the role of furosemide in alleviating cancer-related dyspnea. Weighted mean difference (WMD) was calculated for continuous variables that were reported on the same scale. For continuous data reported in different scales, standardized mean difference (SMD) was calculated. Meta-analysis of three trials yielded a positive effect for opioid administration, WMD _ 1.31[95% CI (_ 2.49) – (_ 0.13)]. Meta-analysis of the six studies showed lack of benefi t to oxygen to improve dyspnea, SMD _ 0.3[95% CI _ 1.06 – 0.47]. The role of benzodiazepines remains unclear, furosemide was not benefi cial. CONCLUSIONS: Our systematic review and meta-analysis demonstrate a benefi cial effect to opioids in alleviating cancer-related dyspnea, and no advantage for the use of oxygen.

2. Clemens KE

This study assessed the effect of opioid treatment on ventilation in dyspneic palliative care patients who received symptomatic treatment with strong opioids. The assessments measured changes in peripheral arterial oxygen saturation (SaO_2), transcutaneous arterial pressure of carbon dioxide ($tcPCO_2$), respiratory rate (f), and pulse rate (PF) during the titration phase with morphine or hydromorphone. The aims of the study were to verify the efficacy of opioids for the management of dyspnea, assess the effect on ventilation, and show whether nasal O_2 insufflation before opioid application leads to a decrease in the intensity of dyspnea. Eleven patients admitted to our palliative care unit were included in this prospective, nonrandomized trial. At admission, all patients suffered from dyspnea. $tcPCO_2$, SaO_2, and PF were measured transcutaneously by means of a SenTec Digital Monitor (SenTec AG, Switzerland). During O_2 insufflation, the intensity of dyspnea did not change. In contrast, the opioid produced a significant improvement in the intensity of dyspnea (P ¼ 0.003). Mean f decreased as early as 30 minutes after the first opioid administration, declining from 41.8 _ 4.7 (35.0e50.0) to 35.5 _ 4.2 (30.0e40.0), and after 90 minutes, to 25.7 _ 4.5 (20.0e32.0) breaths/min. Other monitored respiratory parameters, however, showed no significant changes. There was no opioid-induced respiratory depression.

3. Gomutbutra P.

CONTEXT: Benzodiazepines (BZDs) are commonly prescribed for relief of dyspnea in palliative care, yet few data describe their efficacy. OBJECTIVES: To describe the management of moderate-to-severe dyspnea in palliative care patients. Methods. Chart review of inpatients with moderate or severe dyspnea on initial evaluation by a palliative care service. We recorded dyspnea scores at follow-up (24 hours later) and use of BZDs and opioids. RESULTS: The records of 115 patients were reviewed. The mean age of patients was 64 years and primary diagnoses included cancer (64%, n ¼ 73), heart failure (8%, n ¼ 9), and chronic obstructive pulmonary disease (5%, n ¼ 6). At initial assessment, 73% (n ¼ 84) of the patients had moderate and 27% (n ¼ 31) had severe dyspnea. At follow-up, 74% (n ¼ 85) of patients reported an improvement in their dyspnea, of which 42% (n ¼ 36) had received opioids alone, 37% (n ¼ 31) had BZDs concurrent with opioids, 2% (n ¼ 2) had BZDs alone, and 19% (n ¼ 16) had received neither opioids nor BZDs. Logistic regression analysis identified that patients who received BZDs and opioids had increased odds of improved dyspnea (odds ratio 5.5, 95% CI 1.4, 21.3) compared with those receiving no medications. CONCLUSION: Most patients reported improvement in dyspnea at 24 hours after palliative care service consultation. Consistent with existing evidence,most patients with dyspnea received opioids but only the combination of opioids and BZDs was independently associated with improvement in dyspnea. Further research on the role of BZDs alone and in combination with opioids may lead to better treatments for this distressing symptom.

4. Jennings AL

BACKGROUND: Breathlessness is a common symptom in people with advanced disease. The most effective treatments are aimed at treating the underlying cause of the

breathlessness but this may not be possible and symptomatic treatment is often necessary. Strategies for the symptomatic treatment of breathlessness have never been systematically evaluated. Opioids are commonly used to treat breathlessness: the mechanisms underlying their effectiveness are not completely clear and there have been few good-sized trials in this area.OBJECTIVES: To determine the effectiveness of opioid drugs given by any route in relieving the symptom of breathlessness in patients who are being treated palliatively. SEARCH STRATEGY: An electronic search was carried out of Medline, Embase, Cinahl, the Cochrane library, Dissertation Abstracts, Cancercd and SIGLE. Review articles and reference lists of retrieved articles were hand searched. Date of most recent search: May 1999SELECTION CRITERIA: Randomised double-blind, controlled trials comparing the use of any opioid drug against placebo for the relief of breathlessness were included. Patients with any illness suffering from breathlessness were included and the intervention was any opioid, given by any route, in any dose.DATA COLLECTION AND ANALYSIS: Studies identified by the search were imported into a reference manager database. The full texts of the relevant studies were retrieved and data were independently extracted by two reviewers. Studies were quality scored according to the Jadad scale. The primary outcome measure used was breathlessness and the secondary outcome measure was exercise tolerance. Studies were divided into non-nebulised and nebulised and were analysed both separately and together. A qualitative analysis was carried out of adverse effects of opioids. Where appropriate, meta-analysis was carried out. MAIN RESULTS: Eighteen studies were identified of which nine involved the non-nebulised route of administration and nine the nebulised route. A small but statistically significant positive effect of opioids was seen on breathlessness in the analysis of studies using non-nebulised opioids. There was no statistically significant positive effect seen for exercise tolerance in either group of studies or for breathlessness in the studies using nebulised opioids.REVIEWER'S CONCLUSIONS: There is evidence to support the use of oral or parenteral opioids to palliate breathlessness although numbers of patients involved in the studies were small. No evidence was found to support the use of nebulised opioids. Further research with larger numbers of patients, using standardised protocols and with quality of life measures is needed.

5. Burke AL.

Terminal restlessness is a variant of delirium observed in some patients in their last days of life. Readily reversible causes of restlessness should be identified and treated. Benzodiazepines give effective palliation of this condition, and, unlike haloperidol and the phenothiazines, do not exacerbate the existing tendency to myoclonus and convulsions.

6. AIPO-SICP

La morfina è il farmaco più studiato nel trattamento della dispnea da neoplasia, BPCO avanzata, malattie interstiziali polmonari, insufficienza cardiaca cronica, malattie neurologiche e renali; gli effetti collaterali come la stipsi, sempre presente, la possibile nausea e sonnolenza che prevalgono all'inizio del trattamento, devono essere conosciuti dai medici prescrittori e prevenuti con una posologia personalizzata e con terapie di supporto adeguate.

Con le dosi di morfina utili per trattare la dispnea, il pericolo di una depressione respiratoria clinicamente significativa è poco comune anche negli anziani.

7. Streider M.

BACKGROUND: Dyspnea is a common, very distressing symptom in advanced cancer patients that challenges them, their relatives, and healthcare professionals. This narrative review summarizes important literature dealing with the evidence for opioids, benzodiazepines, oxygen, and steroids for treating dyspnea in advanced cancer patients. METHODS: A selective literature search was undertaken in PubMed, Embase, and the Cochrane Library and extended with literature from the reference lists of included studies up to April 2016. Inclusion criteria were that patients were suffering from advanced cancer and were receiving either opioids, benzodiazepines, corticosteroids, or oxygen. The outcome of interest was the reduction of dyspnea measured via a visual analogue scale (VAS), a numerical rating scale (NRS), or a Borg scale. This narrative review describes in detail the findings of 13 studies. RESULTS: Nine studies deal with the effectiveness of opioids for reducing dyspnea in advanced cancer patients. Five of these found a significant benefit to the use of opioids compared to a placebo. Three found no significant improvements, and two favored combinations of opioids and benzodiazepines. Few high-quality studies were available that used benzodiazepines (n = 3, no difference, significant improvement with midazolam + morphine, significant difference for midazolam) or oxygen (n = 2, both without significant difference). Only one study examined treating dyspnea with steroids in patients with advanced cancer, and that study indicated a benefit of steroids compared to a placebo. CONCLUSIONS: Opioids are the drug of choice for treating refractory dyspnea in advanced cancer patients. Neither benzodiazepines nor oxygen showed signifi- cant benefit. In addition, there is insufficient literature available to draw a conclusion about the effectiveness of steroids for treating persistent dyspnea in advanced cancer patients.

8. Kloke M.

Dyspnoea is a frequent symptom in advanced cancer patients with the highest prevalence in lung cancer (up to 74%) increas- ing in the terminal phase (up to 80%) with major impact on the quality of life of the patient, his or her family, as well as the care- givers [1–5]. Patients describe dyspnoea as suffocating, choking or tightness of breath. Qualitative data have shown that the symptom can be described along three dimensions:

• air hunger—the need to breathe while being unable to increase ventilation;

• effort of breathing—physical tiredness associated with breathing;

• chest tightness—the feeling of constriction and inability to breathe in and out.

In summary, it can be defined as subjective perceived breathless- ness, difficult breathing or shortness of breath. The experience of dyspnoea encompasses physical, as well as psychological, social and spiritual domains [6–8]. Recently, the term ‘total dyspnoea’ has been proposed to capture the complexity of the symptom [9, 10]. Moreover, dyspnoea has

been demonstrated to be one of the most distressing symptoms in cancer patients [11]. This suggests a multidisciplinary approach focusing on the patient's psychological, social and spiritual needs, as well as on the physical symptoms [12–14].

4.8. OCTREOTIDE

USO *OFF-LABEL* CHE SI VUOLE AUTORIZZARE:

1.Somministrazione per trattamento del **vomito nel paziente in fase avanzata di malattia (aspettativa di vita presumibile < 3 mesi).**

2. Somministrazione per per trattamento **dell'occlusione intestinale sintomatica nel paziente in fase avanzata di malattia (aspettativa di vita presumibile < 3 mesi).**

RAZIONALE DELLA RICHIESTA:

1. L'octreotide viene impiegata come terapia standard di prima o seconda linea per l'occlusione intestinale in fase avanzata di malattia in gran parte perché riduce il fluido intraluminale e, così facendo, si presume che **riduca anche il vomito e la nausea nel paziente in fase avanzata di malattia**. Octreotide è più efficace e veloce di ioscina nel ridurre la quantità delle secrezioni gastrointestinali: 100-200 mcg ogni 8 ore sc. In secondo luogo, diminuisce la motilità e i crampi.
2. La gestione **dell'occlusione intestinale nel paziente in fase avanzata di malattia** è clinicamente difficile, poiché i pazienti accusano un'importante sintomatologia che include, in genere, dolore addominale, nausea, vomito e l'incapacità di mangiare. La terapia diretta all'occlusione intestinale nel **paziente in fase avanzata di malattia** deve raggiungere obiettivi palliativi, come ad esempio consentire al paziente ricoverato di tornare a casa, il ripristino della capacità di mangiare, alleviare la distensione addominale, limitare nausea e vomito, e più in generale, migliorare la qualità della vita. Attualmente esiste una vasta gamma di opzioni terapeutiche anche se gli approcci invasivi sono spesso considerate in pazienti che possono riacquistare una qualità di vita accettabile per almeno un periodo di tempo, il processo decisionale è complesso e deve rendere conto di una vasta gamma di fattori sia clinici come il grado di ostruzione, il performance status del paziente, sia soggettivi come gli obiettivi del paziente e della sua famiglia, le sue preferenze. Il trattamento di prima scelta è l'octreotide, ad azione antisecretoria rapida, efficace sulla nausea/vomito e la distensione intestinale, permette spesso di poter togliere il SNG dopo qualche giorno di trattamento. L'octreotide viene impiegata come terapia standard di prima o seconda linea per l'occlusione intestinale in fase avanzata di malattia in gran parte perché riduce il fluido intraluminale e, così facendo, si presume che riduca anche il vomito e la nausea. In secondo luogo, diminuisce la motilità e i crampi.

SITUAZIONE ATTUALE APPROVATA:

Il suo uso è approvato per il controllo sintomatico e riduzione dei livelli plasmatici dell'ormone della crescita (GH) e IGF-1 in pazienti con acromegalia non adeguatamente controllati con terapia chirurgica o radioterapia. Octreotide è anche indicata: nei pazienti acromegalici nei quali l'intervento chirurgico sia controindicato o comunque non accettato o in attesa che la radioterapia raggiunga la massima efficacia; per il trattamento dei sintomi associati a tumori endocrini funzionanti gastro-entero-pancreatici (GEP) come

tumori carcinoidi con caratteristiche della sindrome da carcinoide (vedere paragrafo 5.1 del Riassunto delle Caratteristiche del Prodotto); per la prevenzione delle complicazioni conseguenti ad interventi chirurgici sul pancreas. È utilizzata per il trattamento d'urgenza per bloccare l'emorragia e proteggere dal risanguinamento causati da varici gastro-esofagee in pazienti cirrotici. Octreotide è da utilizzarsi in associazione con uno specifico trattamento come la scleroterapia endoscopica. Per il trattamento di adenomi ipofisari secernenti TSH octreotide è utilizzata:

- quando la secrezione non si normalizza dopo chirurgia e/o radioterapia;
- in pazienti in cui la chirurgia non è appropriata;
- in pazienti irradiati, fino a quando la radioterapia raggiunga l'efficacia.

RICERCA BIBLIOGRAFICA RICHIESTA 1:

Parole chiave: Octreotide, nausea and vomiting in advanced cancer patient

Lavori evidenziati:

1. Gordon P et al. Nausea and vomiting in advanced cancer. *Eur J Pharmacol 2014;* 722:187-191.
2. Gupta M et al. Nausea and vomiting in advanced cancer: the Cleveland Clinic protocol. *J Support Oncol 2013;* 11:8–13.
3. Ang Sk et al: Nausea and vomiting in advanced cancer. American Journal of Hospice Palliative Medicine 27(3) 219-225

RICERCA BIBLIOGRAFICA RICHIESTA 2:

Parole chiave: Octreotide, Malignant Bowel Obstruction, Nausea and vomiting in advanced cancer

Lavori evidenziati:

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7. Berger J et al: Medical Therapy of Malignant Bowel Obstruction With Octreotide, Dexamethasone, and Metoclopramide. Am J Hosp Palliat Care. 2016 May;33(4):407-10. doi: 10.1177/1049909115569047. Epub 2015 Feb 2.
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RCT DISPONIBILI:

No

ABSTRACT RICHIESTA 1:

1. Gordon P.

Nausea and vomiting are very common symptoms in cancer both treatment and non-treatment related. Many complications of advanced cancer such as gastroparesis, bowel and outlet obstructions, and brain tumors may have nausea and vomiting or either symptom alone. In a non-obstructed situation, nausea may be more difficult to manage and is more objectionable to patients. There is little research on management of these symptoms except the literature on chemotherapy induced nausea where guidelines exist. This article will review the etiologies of nausea and vomiting in advanced cancer and the medications which have been used to treat them. An etiology based protocol to approach the symptom is outlined.

2. Gupta M.

Nausea and vomiting are common and distressing symptoms in advanced cancer. Both are multifactorial and cause significant morbidity, nutritional failure, and reduced quality of life. Assessment includes a detailed history, physical examination and investigations for reversible causes. Assessment and management will be influenced by performance status, prognosis, and goals of care. Several drug classes are effective with some having the added benefit of multiple routes of administration. It is our institution's practice to recommend metoclopramide as the first drug with haloperidol as an alternative antiemetic. Dexamethasone should be used for patients with central nervous system metastases or bowel obstruction. If your patient is near death, empiric metoclopramide, haloperidol or chlorpromazine is used without further investigation. For patients with a better prognosis, we exclude reversible causes and use the same first-line antiemetics, metoclopramide and haloperidol. For those who do not respond to first-line single antiemetics, olanzapine is second line and ondansetron is third. Rarely do we use combination therapy or

cannabinoids. Olanzapine as a single agent has a distinct advantage over antiemetic combinations. It improves compliance, reduces drug interactions and has several routes of administration. Antiemetics, anticholinergics, octreotide and dexamethasone are used in combination to treat bowel obstruction. In opiod-naive patients, we prefer haloperidol, glycopyrrolate and an opioid as the first-line treatment and add or substitute octreotide and dexamethasone in those who do not respond. Non-pharmacologic interventions (mechanical stents and percutaneous endoscopic gastrostomy tubes) are used when nausea is refractory to medical management or for home-going management to relieve symptoms, reduce drug costs and rehospitalization.

3. Ang Sk

Nausea and vomiting are relatively common in advanced cancer and is dreaded more than pain by patients. The history, pattern of nausea and vomiting, associated symptoms, and physical examination provides clues as to etiology and may guide therapy. Continuous severe nausea unrelieved by vomiting is usually caused by medications or metabolic abnormalities, while nausea relieved by vomiting or induced by eating is usually due to gastroparesis, gastric outlet obstruction, or small bowel obstruction. Drug choices are empiric or based on etiology. Metoclopramide has the greatest evidence for efficacy followed by phenothiazines and tropisetron. Corticosteroids have not been effective in randomized trials except in the case of bowel obstruction. Treatment of nausea unresponsive to first-line medications involves rotation to medications which bind to multiple receptors (broad-spectrum antiemetics), the addition of another antiemetic to a narrow-spectrum antiemetic (a serotonin receptor antagonist such as tropisetron to a phenothiazine), rotation to a different class of antiemetic (tropisetron for a phenothiazine), or in-class drug rotation. Venting gastrostomy, octreotide, and corticosteroids will reduce nausea and vomiting associated with malignant bowel obstruction.

ABSTRACT RICHIESTA 2:

1. Mercadante S.

The use of symptomatic agents has greatly improved the medical treatment of advanced cancer patients with inoperable bowel obstruction. A systematic review of studies of the most popular drugs used in the medical management of inoperable malignant bowel obstruction was performed to assess the effectiveness of these treatments and provide some lines of evidence. Randomized trials that involved patients with a clinical diagnosis of intestinal obstruction due to advanced cancer treated with these drugs were reviewed. Five reports fulfilled inclusion criteria. Three studies compared octreotide (OC) and hyoscine butylbromide (HB), and two studies compared corticosteroids (CSs) and placebo. Globally, 52 patients received OC, 51 patients received HB, 37 patients received CSs, 15 patients received placebo, and 37 patients received both placebo and CSs. On the basis of these few data, the superiority of OC over HB in relieving gastrointestinal symptoms was evidenced in a total of 103 patients. The latter studies had samples more defined in terms of stage and inoperability, and had a shorter survival in comparison with studies of CSs (less than 61 days, most of them less than 20 days). Data on CSs are less

convincing, due to the methodological weakness of existing studies. This review confirms the difficulties in conducting randomized controlled trials in this population.

2. Mercadante S.

Malignant bowel obstruction (MBO) is a challenging complication of advanced cancer. Conservative treatment of inoperable MBO in terminal cancer patients has been found to be effective in controlling the distressing symptoms caused by this complication in inoperable cancer patients. Twenty years ago, octreotide was proposed to treat symptoms related to malignant bowel obstruction. Since then several reports have confirmed the efficacy of octreotide in the management of gastrointestinal symptoms of MBO. Fifteen randomized controlled trials or observational reports with a significant number of patients treated with octreotide have been reviewed; 281 patients were surveyed. Authors reported a therapeutic success ranging between 60% and 90%. Despite the limited number of controlled studies, the large experience acquired through 20 years suggests that octreotide is the first-choice antisecretory agent for MBO. As such, octreotide is the only drug approved by the health-care system in Italy for this treatment.

3. Ripamonti C.

Malignant bowel obstruction (MBO) is a common and distressing outcome particularly in patients with bowel or gynaecological cancer. Radiological imaging, particularly with CT, is critical in determining the cause of obstruction and possible therapeutic interventions. Although surgery should be the primary treatment for selected patients with MBO, it should not be undertaken routinely in patients known to have poor prognostic criteria for surgical intervention such as intra-abdominal carcinomatosis, poor performance status and massive ascites. A number of treatment options are now available for patients unfit for surgery. Nasogastric drainage should generally only be a temporary measure. Self-expanding metallic stents are an option in malignant obstruction of the gastric outlet, proximal small bowel and colon. Medical measures such as analgesics according to theW.H.O. guidelines provide adequate pain relief. Vomiting may be controlled using anti-secretory drugs or/and anti-emetics. Somatostatin analogues (e.g. octreotide) reduce gastrointestinal secretions very rapidly and have a particularly important role in patients with high obstruction if hyoscine butylbromide fails. A collaborative approach by surgeons and the oncologist and/or palliative care physician as well as an honest discourse between physicians and patients can offer an individualized and appropriate symptom management plan.

4. Gordon P

Nausea and vomiting are very common symptoms in cancer both treatment and non-treatment related. Many complications of advanced cancer such as gastroparesis, bowel and outlet obstructions, and brain tumors may have nausea and vomiting or either symptom alone. In a non-obstructed situation, nausea may be more difficult to manage and is more objectionable to patients. There is little research on management of these

symptoms except the literature on chemotherapy induced nausea where guidelines exist. This article will review the etiologies of nausea and vomiting in advanced cancer and the medications which have been used to treat them. An etiology based protocol to approach the symptom is outlined.

5. Gupta M.

Nausea and vomiting are common and distressing symptoms in advanced cancer. Both are multifactorial and cause significant morbidity, nutritional failure, and reduced quality of life. Assessment includes a detailed history, physical examination and investigations for reversible causes. Assessment and management will be influenced by performance status, prognosis, and goals of care. Several drug classes are effective with some having the added benefit of multiple routes of administration. It is our institution's practice to recommend metoclopramide as the first drug with haloperidol as an alternative antiemetic. Dexamethasone should be used for patients with central nervous system metastases or bowel obstruction. If your patient is near death, empiric metoclopramide, haloperidol or chlorpromazine is used without further investigation. For patients with a better prognosis, we exclude reversible causes and use the same first-line antiemetics, metoclopramide and haloperidol. For those who do not respond to first-line single antiemetics, olanzapine is second line and ondansetron is third. Rarely do we use combination therapy or cannabinoids. Olanzapine as a single agent has a distinct advantage over antiemetic combinations. It improves compliance, reduces drug interactions and has several routes of administration. Antiemetics, anticholinergics, octreotide and dexamethasone are used in combination to treat bowel obstruction. In opiod-na'ive patients, we prefer haloperidol, glycopyrrolate and an opioid as the first-line treatment and add or substitute octreotide and dexamethasone in those who do not respond. Non-pharmacologic interventions (mechanical stents and percutaneous endoscopic gastrostomy tubes) are used when nausea is refractory to medical management or for home-going management to relieve symptoms, reduce drug costs and rehospitalization.

6. Watari H.

OBJECTIVE: Malignant bowel obstruction (MBO), of which symptoms lead to a poor quality of life, is a common and distressing clinical complication in advanced gynecologic cancer. The aim of this study was to prospectively assess the clinical efficacy of octreotide to control vomiting in patients with advanced gynecologic cancer with inoperable gastrointestinal obstruction. METHODS: Patients with advanced gynecologic cancer, who presented at least one episode of vomiting per day due to MBO, were enrolled in this prospective study from 2006 to 2009. Octreotide was administered when necessary at doses starting with 300 μg up to 600 μg a day by continuous infusion for 2 weeks. Primary end point was vomiting control, which was evaluated by common terminology criteria for adverse events version 3 (CTCAE v3.0). Adverse events were also evaluated by CTCAE v3.0. RESULTS: Twenty-two cases were enrolled in this study. Octreotide controlled vomiting in 15 cases (68.2%) to grade 0 and 3 cases (13.6%) to grade 1 on CTCAE v3.0. Overall response rate to octreotide treatment was 81.8% in our patients' cohort. Among 14 cases without nasogastric tube, the overall response rate was 93.1% (13/14). Among 8 cases with nasogastric tube, 4 cases were free of tube with decrease of drainage, and

overall response rate was 62.5% (5/8). No major adverse events related to octreotide were reported. CONCLUSIONS: We conclude that 300-μg/d dose of octreotide was effective and safe for Japanese patients with MBO by advanced gynecologic cancer. Octreotide could contribute to better quality of life by avoiding placement of nasogastric tube.

7. Berger J.

BACKGROUND: Malignant bowel obstruction is a highly symptomatic, often recurrent, and sometimes refractory condition in patients with intra-abdominal tumor burden. Gastro-intestinal symptoms and function may improve with anti-inflammatory,anti-secretory, and prokinetic/anti-nausea combination medical therapy.OBJECTIVE: To describe the effect of octreotide, metoclopramide, and dexamethasone in combination on symptom burden and bowel function in patients with malignant bowel obstruction and dysfunction.DESIGN: A retrospective case series of patients with malignant bowel obstruction (MBO) and malignant bowel dysfunction (MBD) treated by a palliative care consultation service with octreotide, metoclopramide, and dexamethasone. Outcomes measures were nausea, pain, and time to resumption of oral intake. RESULTS: 12 cases with MBO, 11 had moderate/severe nausea on presentation. 100% of these had improvement in nausea by treatment day #1. 100% of patients with moderate/severe pain improved to tolerable level by treatment day #1. The median time to resumption of oral intake was 2 days (range 1-6 days) in the 8 cases with evaluable data. Of 7 cases with MBD, 6 had For patients with malignant bowel dysfunction, of those with moderate/severe nausea. 5 of 6 had subjective improvement by day#1. Moderate/severe pain improved to tolerable levels in 5/6 by day #1. Of the 4 cases with evaluable data on resumption of PO intake, time to resume PO ranged from 1-4 days. CONCLUSION: Combination medical therapy may provide rapid improvement in symptoms associated with malignant bowel obstruction and dysfunction.

8. Faisinger RL

The inadequacy of prolonged conservative management with nasogastric suction and intravenous fluids for terminally ill patients with bowel obstruction has long been recognized. Using previous reports and our experience on the Palliative Care Unit at the Edmonton General Hospital, we have developed a basic approach to bowel obstruction management. In a review of 100 consecutive patients who died on our Palliative Care Unit, 15 required medical management for bowel obstruction. Evaluation of these cases suggests that intensive medical management can provide good symptom control without using intravenous lines and with minimal use of nasogastric tubes.

9. Krouse RS

There is a dearth of well-designed clinical research focusing on palliative care in cancer patients, especially those who are near the end of life. Reasons for this include ethical dilemmas in conducting such trials, communication barriers between specialties, and unclear standards for best care practices. To ensure that patients with incurable illnesses are offered the best available care, it is essential to develop and disseminate research

methodologies well suited to this population. Given the multidimensional and culture-dependent nature of the end-of-life experience, it is necessary to adopt an interdisciplinary approach to developing research methods. As a means of initiating the process of palliative clinical research methodology development, malignant bowel obstruction (MBO) was used as a model to develop a research protocol. Although many treatment options for MBO have been proposed, existing literature offers little guidance with regard to algorithms for optimal management. To this end, an international leaders in quality-of-life research, ethnocultural variability, palliative medicine, surgical oncology, gastroenterology, major consortium research, medical ethics, and patient advocacy/cancer survivors was convened in Pasadena, California, on November 12-13, 2004. Participants also represented the broad ethnic and racial perspectives required to develop culturally sensitive research methods. Consensus on methodological approaches was attained through vigorous debate. Using the conference-developed MBO model to implement trials will advance palliative care research.

5. NOTE

Valorizzazione numerica dei pazienti trattati con terapia off-label, tempistiche medie di trattamento e un primo approccio di valutazione economica dell'impatto sul SSN.

Fino a qualche anno fa non erano ancora disponibili stime consolidate, nazionali ed internazionali, rispetto ai bisogni di Cure Palliative nella popolazione. Ad oggi, questi dati sono disponibili grazie a documenti redatti dall'Organizzazione Mondiale della Sanità[(1)] e a molteplici pubblicazioni autorevoli sulla letteratura internazionale[(2-3)].

Si ritiene, quindi, attulamente possibile proporre una stima attendibile dei bisogni nella popolazione del nostro Paese. In particolare si può verosimilmente individuare il bisogno di cure palliative specialistiche, normalmente riferite a malati nella fase finale di vita, che necessitano di terapie per il controllo dei sintomi e, di conseguenza, anche di farmaci *off-label.*

Secondo quanto definito dall'OMS e dalle più recenti stime pubblicate a livello internazionale (comprendenti anche la realtà italiana), pur tenendo conto di una variabilità della definizione di "adulto" (>= 15 anni nelle stime OMS e >=18 anni in altre stime), il bisogno per l'Italia è stimato complessivamente fra le 300.000 e le 400.000 persone che ogni anno muoiono con necessità di cure palliative durante l'ultimo periodo della loro vita. Questo bisogno può essere quindi calcolato[(1)] in circa 560 persone/anno ogni 100.000 adulti residenti o in una percentuale compresa fra il 70% e l'80% di tutti i morti/anno[(3)]. Di questo numero complessivo di persone, il 60% è affetto da patologie diverse dal cancro e il 40% da patologie di origine neoplastica. È da sottolineare che la risposta a questo bisogno deve essere modulata con modalità organizzative differenziate e con diversi livelli di intensità assistenziale: un "approccio palliativo" di qualità, che dovrebbe essere garantito da tutti i professionisti della salute, in particolare dai medici indipendentemente dalla loro specialità, e "cure palliative specialistiche" erogate nell'ambito di una Rete di Cure Palliative che si occupa di questi malati in ospedale, a domicilio (cure palliative domiciliari di base e specialistiche) e in hospice. Dall'Organizzazione Mondiale della Sanità, per quanto riguarda i Paesi a elevato reddito, è stata anche proposta[(1)] una stima del rapporto fra questi due livelli di risposta al bisogno: il 30-45% delle persone con bisogni di cure palliative nel loro ultimo periodo di vita deve trovare risposta a questi bisogni con la garanzia di poter accedere a cure palliative specialistiche (nei diversi setting di cura), mentre per la parte restante di questa popolazione il bisogno può trovare risposte adeguate in un "approccio palliativo" di qualità, non necessariamente specialistico. Queste stime sembrano trovare una conferma importante anche nei risultati preliminari di progetti di ricerca conclusi recentemente nel nostro Paese.

Relativamente alla valorizzazione numerica dei pazienti adulti che potrebbero essere trattati con terapie *off-label* potremmo far riferimento al campione dei soggetti che necessitano di cure palliative specialistiche. Si potrebbe considerare quindi solo il 30-45% delle persone che complessivamente necessitano di cure palliative (di base e specialistiche).

I dati Istat del 2014 riportano in Italia 598.670 decessi, con un tasso standardizzato di mortalità di 85,3 individui per 10mila residenti.

In base a quanto riportato sopra, le persone che necessitano di cure palliative

specialistiche sono quindi in Italia 188.000, circa il 31% dei deceduti.

Se il dato relativo al numero di pazienti che necessita di cure palliative specialistiche è un dato realistico e supportato dalla letteratura scientifica, rimane più difficile quantificare il numero delle persone che è sottoposto a terapie *off-label* e, ancor meno, stabilire le tempistiche di trattamento.

In Italia esiste solo uno studio in letteratura[4] nel quale si riporta che il 4.5% di tutte le prescrizioni è *off-label* e, di questa percentuale, il 25.2% lo è per indicazione e l'85.4% per via di somministrazione (sottocutanea).

Può senz'altro essere utile valutare i tempi di degenza media in hospice e a domicilio (circa 20 giorni in hospice e 45 giorni a domicilio) per avere un quadro generale sui tempi di trattamento, considerando che molti dei farmaci sono utilizzati solo negli ultimi giorni di vita.

Valutazione economica

Questo tipo di valutazione è complessa, ma si può affermare che la pratica *off-label* in cure palliative sia molto diffusa ed i farmaci utilizzati siano poco costosi, se si esclude la octreotide che comunque può essere sostituita dalla joscina metilbromuro.

L'utilizzo dei farmaci *off-label* per i quali si richiede l'autorizzazione all'inserimento nell'elenco dei medicinali istituito con la Legge 648/96, è ormai una prassi consolidata e si riferisce a farmaci che di fatto sono già a carico del SSN.

Si ritiene che l'inserimento formale di queste molecole nell'elenco della Legge 648/96 non comporterebbe incrementi di spesa se non per un probabile, ma modesto aumento del loro impiego conseguente alla formalizzazione dell'utilizzo. Molto probabilmente, invece, questo aumento farebbe diminuire l'uso di altri farmaci più costosi e meno efficaci.

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