Reflections on palliative sedation

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Abstract: 'Palliation sedation' is a widely used term to describe the intentional administration of sedatives to reduce a dying person's consciousness to relieve intolerable suffering from refractory symptoms. Research studies generally focus on either 'continuous sedation until death' or 'continuous deep sedation'. It is not always clear whether instances of secondary sedation (i.e. caused by specific symptom management) have been excluded. Continuous deep sedation is controversial because it ends a person's 'biographical life' (the ability to interact meaningfully with other people) and shortens 'biological life'. Ethically, continuous deep sedation is an exceptional last resort measure. Studies suggest that continuous deep sedation has become 'normalized' in some countries and some palliative care services. Of concern is the dissonance between guidelines and practice. At the extreme, there are reports of continuous deep sedation which are best described as non-voluntary (unrequested) euthanasia. Other major concerns relate to its use for solely non-physical (existential) reasons, the under-diagnosis of delirium and its mistreatment, and not appreciating that unresponsiveness is not the same as unconsciousness (unawareness). Ideally, a multiprofessional palliative care team should be involved before proceeding to continuous deep sedation. Good palliative care greatly reduces the need for continuous deep sedation.

Keywords: Palliative sedation, continuous sedation until death, continuous deep sedation

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Introduction

Nearly 30 years ago, the Division of Pain Therapy and Palliative Care at the National Cancer Institute in Milan reported that of patients cared for at home, 63 out of 120 patients had unendurable symptoms which were relieved only by sedation-inducing sleep.[1] On average, such symptoms appeared 2 days before death. Other centres indicated that this was not their experience,[2,3] and thus began an ongoing discussion about sedation at the end of life.[4,5]

Initially referred to as 'terminal sedation',[6] the term fell into disrepute because of potential ambiguity: did the word 'terminal' relate to the patient or the sedation? 'Palliative sedation' (PS) was considered preferable because it emphasized that the aim was palliation (to relieve symptoms) and not to terminate life and was defined as follows:

> The intentional administration of sedative drugs in dosages and combinations required to reduce the consciousness of a terminal patient as much as necessary to adequately relieve one or more refractory symptoms.[7]

The definition implies proportionality (a fundamental ethical consideration) and deliberately made no distinction between continuous and intermittent, and light and deep sedation. Subsequent variants refer to either 'dying patients' or 'imminently dying patients' rather than 'terminal patients', and additional clarity is introduced by stating explicitly that 'refractory symptoms' means 'intolerable suffering caused by refractory symptoms'.[8–10]

According to one review, there are over 50 variant definitions in the literature.[4] However, all guidelines reflect the original definition, and stress that PS implies an *intended* reduction in consciousness and *excludes sedation secondary to symptom control measures*.[11–13] Although they refer briefly to intermittent (respite) sedation, the focus is always on continuous sedation.

Table 1. Sedation for intolerable refractory symptoms.

	Palliative sedation	*CSD* (continuous sedation until death)	CDS (continuous deep sedation)
Short prognosis	+	+	+
Intended (primary)	+	+	+
Continuous?	–/+	+	+
Deep?	–/+	–/+	+

The main focus in this article is on continuous deep sedation (CDS). Unlike intermittent and light sedation, CDS is ethically controversial because it ends a person's 'biographical life' (the ability to interact meaningfully with other people) and, if prolonged, shortens 'biological life'.[14–16] Family concerns,[17] sedation in children[18,19] and in Intensive Care Units[20] will not be discussed.

Interpreting the literature

In quantitative systematic reviews, a clear distinction is not always made between primary intended sedation and secondary sedation, or between light and deep, intermittent and continuous, progressive (proportionate) and precipitous (sudden) sedation. For example, in the Cochrane systematic review entitled 'Palliative pharmacological sedation for terminally ill adults',[21] three of the 14 studies were general articles about the use of sedatives in dying patients. Two included all patients who, at some point in the last week of life, received a sedative in any dose and any frequency or above a certain threshold.[22,23] In one of these, sedatives were prescribed for 68 out of 102 patients, for whom 'sublingual lorazepam tablets and clonazepam drops were commonly used and efficacious.'[23] (This appears to be the source of the figure quoted elsewhere that up to 67% of dying patients may need PS.) The third study[24] was limited to the last 2 days of life, and the treatment of none of the patients merited the term 'palliative sedation' (L Radha Krishna, personal communication, 2015).

A report about *night sedation* with intravenous (IV) midazolam in two patients with cancer for 4 weeks and 4 months respectively, described this as 'long-term intermittent palliative sedation'.[25] The refractory insomnia ± delirium was relieved by the night sedation, and daytime pain scores reduced from 8–10/10 to 2–3/10. However, sedatives for sleep disorders are *not* generally regarded as PS.[26]

More surprising is the report from a palliative care unit (PCU) in the United States which states that 23% of 186 patients who received PS were discharged alive.[27] Possibly, the reason for this relates to a hospital policy which dictates that, apart from anaesthesia, intensive care and the one-off use for procedures, midazolam use is restricted to PS under the direction of the PCU. Thus, any patient prescribed parenteral midazolam is automatically recorded as having received PS.

Continuous sedation until death (*CSD*) and CDS are more precise terms and thus are preferable. Both exclude intermittent sedation and CDS exclude all but deep sedation (Table 1) However, there is still potential for confusion unless:

1. It is appreciated that *CSD* (depth unstated; used more in qualitative studies[4,28]) and CDS (used more in quantitative studies[29,30]) are *not* synonymous
2. A clear distinction is made between primary intended sedation and secondary sedation.

Some authors have differentiated between proportionate palliative sedation (PPS) and palliative sedation to unconsciousness (PSU),[31,32] also called 'gradual CDS' and 'rapid CDS'.[30] PPS implies progressive sedation according to need, and PSU implies rapid induction of deep sedation. However, because ethically all sedation is justified by necessity, and thus should be proportionate (whatever the rate of onset), this distinction is unhelpful, and best avoided.[33]

Several clinical scales are available to record the depth of sedation. The Richmond Agitation-Sedation Scale (RASS) is widely used, with scores from +4 (combative) to −5 (unrousable).[34] Deep

sedation (−4) means no response to voice, but any movement to physical stimulation; and unrousable (−5) means no response to voice or physical stimulation; CDS embraces both these categories.

In contrast, *CSD* is broad enough to encompass a spectrum of clinical practices. This is illustrated in the results of the international UNBIASED study which compared *CSD* at the end of life in the United Kingdom, the Netherlands and Belgium.[35] Big differences were noted. For example, in Belgium and the Netherlands, rapid induction of deep sedation until death is the norm[36] and is sometimes organized like euthanasia (legal in both countries), with a family farewell before the patient is rendered permanently unrousable.[37] This is partly because of pressure from relatives to hasten death,[37] and an understanding that, regardless of necessity, 'if the patient is still here tomorrow, we will double the dose … the patient is not awake anymore, what is the point of letting her lie here for days?' (PC Consult Team nurse).[38] In contrast, in the United Kingdom, clinical practice tends to reflect the 'framework' for PS produced by the European Association for Palliative Care,[12] where the emphasis is on titrating doses proportionately against symptoms, maintaining awareness if possible.

The differences in practice noted between the United Kingdom on the one hand and the Netherlands and Belgium on the other are reflected in the approach to decision-making about *CSD*.[39] At one end of the spectrum (mostly in the United Kingdom), doctors discuss the possible need for sedation with the patient but take the decision themselves. At the other end (mostly in the Netherlands and Belgium), the patient initiates the conversation and the doctor's role is mainly limited to evaluating if and when the medical criteria in the guidelines are met.

The contrast is further reflected in the language used about sedation. In one study, many Belgian and Dutch doctors and nurses referred to 'palliative sedation' or 'terminal sedation', whereas these terms were not mentioned by any of the UK participants. In fact, many of the latter reported feeling uncomfortable with the word 'sedation', preferring to talk about 'making the patient more comfortable'[37]:

> I haven't given anyone continuous sedation; there have been lots of patients … agitated at the end of their lives and … it's appropriate to give medications to relieve that agitation and that restlessness, so we are giving drugs that have sedative effects but the aim is … to relieve that agitation and restlessness. (UK hospice doctor)[36]

The situation in France is distinct, unique and evolving. In 2016, the Claeys–Leonetti law was enacted which gives patients with 'severe and incurable disease which is refractory to treatment and is life-threatening in the short-term' the explicit right to CDS until death (SPCMD, la sédation profonde et continue maintenue jusqu'au décès) and the withdrawal of all life-sustaining treatment.[40] Patients receiving CDS will not normally receive artificial nutrition or hydration, and hospitals must to keep a record of all cases. In no other country do patients have a legal right to CDS, albeit limited to those with a short prognosis.

In 2018, the Haute Autorité de Santé published guidance on the application of the law.[41] This seeks to clarify the limits of the law by detailing typical implementation. For example, although the law does not define the shortness of the prognosis, the guidance does (Box 1). It is still too soon to know how the law will work out in practice, but it seems that most requests are for rapid-onset CDS rather than proportionate sedation (M Filbet, personal communication, 2018).

CDS can also be requested 'to avoid all suffering' (e.g. before ventilator withdrawal), not just to relieve present suffering. In addition, unless a patient with impaired cognitive function had previously stated that they would not want it (e.g. in an Advanced Directive), CDS is permissible if there are signs of suffering after life-sustaining measures have been discontinued and after a 'collegial procedure' has confirmed that all the necessary prerequisites have been met.[40,41]

Normal or exceptional treatment?

Doctors have a fundamental ethical responsibility to ease suffering, particularly when intolerable and in those close to death. Thus, there must be a strong possibility that there will be occasions when CDS can be justified on the grounds of necessity. As such, it could be reasonable to consider CDS as 'normal' treatment. Indeed, the Royal Dutch Medical Association's guidelines for PS state that it is both 'normal' and 'radical'.[13] However, from an ethical point of view, because it means the end of a person's biographical (social) life, it is always

Box 1.

Extract from: Comment mettre en œuvre une sédation profonde et continue maintenue jusqu'au décès?[41] (How to approach the question of CDS until death).

Le pronostic est-il engagé à court terme?
(Is the prognosis short-term?)
Si le décès est proche, attendu *dans les quelques heures ou quelques jours*, une SPCMD peut être envisage.
(If death is close, expected within a few hours or a few days, CDS can be considered.)
Si le décès est attendu dans *un délai supérieur à quelques jours* et que les symptômes sont réfractaires, *une sédation réversible de profondeur proportionnée* au besoin de soulagement est discutée avec le patient.
(If death is expected after a delay of more than a few days and the symptoms are refractory, if need be discuss deep proportionate reversible sedation with the patient.)

an *exceptional last resort measure* and should not be considered routine or the default option.[42] Consequently, concern has been expressed that 'normalization' could result in the ethical aspects of PS being ignored or glossed over.[43]

For example, given that ethically it is an exceptional last resort measure, should CDS be permitted only if the patient has been seen by and cared for by a palliative care team?[44,45] The Dutch guidelines are ambiguous about this:

> The committee sees no reason to impose the condition that the physician with specific expertise must always be consulted before making the decision to administer PS. (p.7)

> Continuous sedation within the context of PC is highly complex and requires specialist knowledge … The committee advises physicians to consult the appropriate expert(s) with specialist knowledge of PC in good time. (p.8)[13]

A report from the Netherlands showed that when a PC team was consulted by phone, it was deemed inappropriate to proceed with PS in 47/113 (41%) of cases.[46] Thus, if our collective aim as clinicians is to minimize the need for ethically exceptional measures, there seems to be a strong case for mandating referral to a specialist PC service before proceeding to CDS.[45]

Incidence of CDS

Reports of the incidence of CDS fall into two categories:

1. Those derived from country-wide surveys (either one-off reports or sequential reports over many years).
2. Those from PC services (either home care programmes or inpatient units).

Table 2. Selected end-of-life practices in the Netherlands 2001–2015.[49]

	2001	2005	2010	2015
Continuous deep sedation	–	8.2	12.3	18.3
Physician-assisted suicide	0.2	0.1	0.1	0.1
Euthanasia	2.6	1.7	2.8	4.5
Ending of life without explicit patient request	0.7	0.4	0.2	0.3

A report in 2006 from six European countries gave a range of 2.5–8.5%,[47] and, a few years later, a report from the United Kingdom gave a figure of almost 19%.[48] Sequential data are available from the Netherlands (Table 2),[49] Belgium (Table 3)[50] and Switzerland. In the Netherlands, PS has become increasingly common and is now associated with >18% of all non-sudden deaths. In neighbouring Flanders (Belgium), the incidence is lower (12%), having fallen from a peak of 14.5%. A dramatic increase has been reported in Switzerland: 6.7% in 2001 to almost 25% in 2013. As in the Netherlands, most CDS is home-based supervised by the family practitioner.[51]

The incidence of CDS reported from specialist PC services ranges up to 15%[52] (and *CSD* up to 55%).[53–55] In contrast, at one PCU in Belgium, the incidence of CDS fell from 7% to 2.5% over 6 years.[56] The decrease was attributed to an

Table 3. Selected end-of-life practices in the Flanders (Belgium) 1998–2013.[50]

	1998	2001	2007	2013
Continuous deep sedation	–	8.2	14.5	12.0
Physician-assisted suicide	0.12	0.01	0.07	0.05
Euthanasia	1.1	0.3	1.9	4.6
Hastening of death without explicit patient request	3.2	1.5	1.8	1.7

Table 4. Common refractory symptoms resulting in *CSD*/CDS (%).

	Delirium	Dyspnoea	Pain
Ventafridda and colleagues (1990)[1]	17	52	49
Mercadante and colleagues (2014)[61]	83	17	0

CSD: continuous sedation until death; CDS: continuous deep sedation.

improved standard of palliative care and a team approach to decision-making. In a PCU in Japan, the incidence is even lower, namely 1.4%.[44]

Guidelines

Guidelines for *CSD* differ in several important respects.[8,9] Whereas some stress that death should be expected within hours or a few days ('imminently dying'),[11] others state 'less than two weeks'.[13] This allows for widely differing practices. One purpose of the time limit is to emphasize that the intention underlying *CSD* is the relief of suffering and not to cause death.

The recommended framework for sedation of the European Association for Palliative Care[12] has been described as a series of uneasy compromises, more a harm reduction strategy than guidelines for optimal practices.[57] Concerns over practice in Belgium and the Netherlands seem to underlie the framework but are not discussed explicitly. However, the biggest shortcoming of many of the guidelines is the emphasis on the use of midazolam, despite noting that the main indication for *CSD* is delirium (see below).

The length of the guidelines differs. Although summarized on seven pages, those of the Royal Dutch Medical Association extend to 78 pages, partly because of a need to differentiate between PS (regarded as radical but normal treatment) and euthanasia (regarded as exceptional treatment requiring legal regulation).[13] In contrast, those of the Norwegian Medical Association comprise just two pages.[58] Although the detail in the former is much greater than in the latter, longer does not necessarily mean better, particularly if largely based on 'expert opinion'.[57] Furthermore,

> Algorithms that reduce patient care into a sequence of binary (yes/no) decisions often do injustice to the complexities of medicine.[59]

Uncritical use of guidelines can result in a 'one-size-fits-all' mentality and could lower rather than raise the standard of symptom-specific management:

> We definitely follow the rules … So the prognosis has to be <2 weeks, with refractory symptoms. And sometimes I think we have to wait too long … So when she got the itch we could do nothing about, I thought hooray now we can do sedation. (Dutch hospital doctor reflecting on the care of a woman with renal cancer)[36]

The need for informed consent features in all guidelines. However, particularly because of delirium, many patients will no longer be able to give valid consent. Thus, family or health proxy consent will generally be the norm.[55] Seeking *informal assent* rather than *formal consent* is probably the most practical option.[60]

Indications for *CSD*

The commonest intractable symptoms associated with *CSD* are delirium, dyspnoea and pain. Other symptoms include fatigue, agitation and existential distress. However, their published incidence varies widely (Table 4). The more recent percentages are typical of more recent reports, suggesting that, in some centres, delirium may well be under-diagnosed and pain management not always optimal (Table 4). Indeed, the two are probably linked, with the

intractable pain being part of an unrecognized and untreated delirium. For example,

> At night, he changed completely. He became aggressive … We went through escalating doses of ketamine [for pain], added in clonazepam, and opioids, and we just didn't seem to be getting anywhere. And this behaviour began to encroach into the day as well. Even with phenobarbital it wasn't a quick, easy solution. (UK hospice nurse)[36]

Progressive organ failure in the last days of life will impact on cognition and emotion and often precipitates delirium. If the agitation is interpreted as existential distress and treated with a benzodiazepine (which alone generally exacerbates delirium[62]), it is easy to see how a vicious medicinal downward spiral can ensue: more distress → more midazolam → more agitation → more midazolam until the patient is deeply sedated – unnecessarily.

CSD/CDS for existential distress

'Existential' refers to issues surrounding meaning and purpose in life. However, in relation to *CSD*/CDS, the term 'existential distress' (or 'psycho-existential distress') has been used more widely to embrace a range of psychological symptoms:

1. A profound sense of meaninglessness/worthlessness;
2. Despair/anguish/hopelessness;
3. Remorse and regret;
4. Death anxiety/fear of death;
5. Feeling a burden on others;
6. Loss of control/dependency;
7. Dependency/loss of dignity;
8. Lack of social support/isolation.[63–65]

By convention, it excludes depression, delirium and anxiety disorders.

Like pain, distress is what the patient says it is. It is subjective and cannot be measured objectively. Bodies do not suffer; human beings do.[66] Thus, in a nationwide study in Dutch nursing homes (continuing care hospitals), out of >300 patients who received *CSD*, existential distress was noted in >25%.[64] However, in only one patient (0.3%) was existential distress given as the sole reason.

In a report from a PCU in Japan, only one of 248 patients (0.4%) received sedation solely for existential distress.[67] However, this was mainly enhanced night sedation until the patient's death 2 weeks later; it did *not* progress to CDS. During this time, the patient could take some food and fluid and communicate verbally with her family:

> A 61-year-old woman with rectal cancer repeatedly expressed the desire for death. Physical discomfort was minimal. Dependency was the main reason for her profound distress: she wished to die on the day of her choice. CDS was deemed unacceptable because her estimated prognosis was >6 weeks. She continued to receive psychological support, and agreed to (a) a trial of a psychostimulant and (b), after depression was diagnosed, a trial of an antidepressant but without apparent benefit. After 7 weeks, the multiprofessional team agreed that she now met the criteria for PS. This began with sedation only at night with a subcutaneous infusion of midazolam 2–6 mg/h with additional intramuscular levomepromazine 12.5–25 mg (frequency not stated). She was allowed to take triazolam (a night sedative) 0.25 mg during the day 'whenever she wanted'. After 6 days she stated that the situation was more acceptable; she died 8 days later in her sleep, probably from pneumonia.[67]

A subsequent Japanese nationwide survey of nearly 9000 patients in 81 PCUs, only 90 (1%) had CDS because of refractory existential distress.[63] Where the duration of the sedation was reported, 63% died in <1 week (thus had been 'imminently dying'); 35% died in 1–3 weeks and one patient survived >1month.

All guidelines express caution about *CSD*/CDS for solely existential reasons. The Dutch guidelines specifically exclude it,[13] and the Ethics Committee of the United States' National Hospice and Palliative Care Organization was unable to achieve consensus.[68] The reasons for the caution and/or opposition are as follows:

1. The presence of severe existential symptoms alone does *not* indicate imminent death – this being an essential criterion for *CSD*/CDS.[12]
2. It is likely that death will be from the complications of dehydration ± infection, and not the underlying disease.[69]
3. It is almost impossible to be sure that existential distress is refractory; the severity of the distress is typically very variable, and psychological adaptation and coping is the norm.[15,70]
4. Standard (non-drug) treatments have low intrinsic morbidity, and a high chance of achieving significant amelioration.[70]

Consequently, it is ethically imperative that clear criteria are agreed and adhered to:

1. If the patient is *not* imminently dying, *CSD*/CDS is *not* permissible
2. The designation of refractoriness should be made only after *skilled* psychiatric/psychological evaluation has excluded depression, delirium and an anxiety disorder, and appropriate measures have failed to help the patient move to a more positive outlook.[70]
3. Initially, sedation should be on an intermittent (respite) basis, *not* continuous (see below).[12,63]
4. As always, sedation should be proportionate, and progressive only if distress persists.[67,71]
5. The decision to proceed to *CSD* must be a multiprofessional team decision; individual feelings inevitably bias decision-making.[72]

In the Japanese study of CDS for existential suffering, only 59% received specialist psychological, psychiatric or religious support. However, 94% had at least one episode of intermittent (respite) sedation before progressing to CDS.[63]

Guidelines typically refer to periods of respite sedation of 1–2 days. However, adequate night sedation is an important first step – as demonstrated in the case history above (p.6) and the report about 'long-term intermittent PS' earlier in this article (p.2).[25]

In my own clinical practice, the next step would be the offer of additional night sedation after lunch. Thus, to a patient who expresses ongoing distress about not being able to cope, I might say something along the lines of:

> Being ill is hard work … Given your depleted physical and psychological reserves, being awake for 16 hours is too long … We need to break the day up … I suggest we start by giving you a night sedative after lunch to allow you to sleep for 3-4 hours – and wake refreshed and more able to enjoy your visitors in the evening.

In practice, such an offer would have been made only to patients with a poor performance status (e.g. more or less bedfast) and a relatively short (though undefined) prognosis. I never thought of it as PS, just appropriate intermittent sedation.

Ethical discussion about CDS for existential distress will inevitably extend to a consideration of the most fundamental questions about human existence[73]:

1. What is the essence of human nature?
2. What comprises personhood?
3. What are the meaning and purpose of suffering, if any?[74]
4. What can we learn from Near Death Experiences and deathbed visions?[75]
5. Does consciousness survive beyond physical death?

Our answers to these questions will almost certainly impact on our attitude to CDS for existential distress. These questions cannot be addressed solely from a medical perspective; they demand an interdisciplinary and multiprofessional approach.[73]

Clinically assisted hydration

As in all areas of medicine and with any intervention, it is necessary to weigh up the potential benefits and the possible harms. Because palliative care is fundamentally about quality of life, there should be an ever-present undercurrent of concern that interventions are not just prolonging the process of dying. Traditionally, there has been a reluctance to introduce tubes and drips (parenteral infusions) when someone is clearly dying, as evidenced (among other things) by a progressive disinterest in food and fluid. Most palliative care clinicians will probably hesitate before resorting to clinically assisted hydration (CAH).

This issue is addressed in all guidelines. Those of the Norwegian Medical Association state that parenteral infusion is *not* normally indicated if the patient has stopped drinking before sedation is started but is indicated if the patient was taking fluids in any significant amount (e.g. ⩾500 ml/24 h) or was receiving parenteral fluids before PS was started.[58]

If CAH is introduced, its use should be kept under review and stopped if it appears to be causing harm. Nutrition is generally a non-issue because most patients who are potential candidates for PS will have mostly or completely stopped eating.

The use of CAH in CDS varies between countries. For example, in the past in Belgium and Italy about 2/3 received CAH, compared with about 1/3 in the Netherlands.[47] More recent Belgian data indicate that now only about 1/4 of

patients receive CAH, with the majority continuing until death.[76] Since the publication of the national Dutch guidelines for PS (which discourages CAH), the proportion of patients receiving CAH has fallen further.[77]

Does PS shorten survival?

Most studies report no difference in survival between patients receiving PS and those not. The measure generally used for comparison is survival from *the time of enrolment into a PC programme until death*.[52,78] However, to me, this measure lacks face validity, and thus is essentially meaningless. In addition, apart from one study,[79] no steps were taken to match the characteristics of the two groups, and the depth of sedation is not always taken into account. Indeed, using this measure, some studies have even shown a significantly longer survival in patients receiving PS than in those who did not (Table 5).[55,80]

The depth of sedation is perhaps the most important factor in relation to length of survival. It is known from routine anaesthetic and intensive care practice that CDS (RASS –4 to −5) sets in motion predictable self-perpetuating negative neurological, cardiovascular, respiratory and metabolic effects because of its depressant effect on the brain-stem.[4] Without systemic medical interventions (standard practice during anaesthesia and intensive care), patients will predictably and inevitably progress to cardiovascular and respiratory collapse and death, particularly if CDS is rapidly induced. A hint that this is the case can be found in a Japanese study in which significant cardiopulmonary suppression was reported in 20% and was considered to have been fatal in 4%.[81]

Thus, even if PS in all its varieties was to be definitely shown not to reduce mean survival, CDS certainly does. This, of course, is why *CSD* should be proportionate and progressive, and *not* CDS from the start. In other words, CDS must be justified by necessity, lighter levels of sedation having proved inadequate.

Most studies report short survival times after the start of PS/CDS, for example, with a median survival of about one day.[55] Reports of occasional patients who survive PS for 2–3 weeks probably have *not* been deeply sedated for much of that time and may have been receiving CAH. The subacute effects of prolonged sedation relate to the onset of metabolic stress caused by water and nutritional deprivation (in the absence of CAH); and to infection, commonly pneumonia secondary to pulmonary aspiration (regardless of hydration/dehydration) (M Rady, personal communication, 2018).

Table 5. Mean duration of survival from time of admission to inpatient or home care palliative care service (both Sicilian studies).

Palliative sedation	Inpatient[55]	Home care[80]
No	3.3 days	35 days
Yes	6.6 days	38 days
Is difference significant?	Yes, $p = 0.003$	No, $p = 0.98$

Choice of drugs

Given that delirium is the most common indication for *CSD*,[78] it is disturbing that most guidelines promote midazolam as the sedative of first choice. A notable exception is the guideline of the Spanish Society for Palliative Care (2005) which differentiates clearly between sedation in patients with delirium and those without. For the former, an antipsychotic (haloperidol, progressing to levomepromazine) is recommended as first-line treatment, with midazolam recommended in other circumstances.[82] The second most common reason for *CSD* is extreme breathlessness.[78] Although midazolam may settle the associated fear and agitation, morphine and midazolam together provide maximum benefit.[83]

At some centres, notably in the United States, lorazepam is used instead of midazolam.[84] Third-line drugs generally comprise phenobarbital[85] or profofol.[86–88] Surprisingly, morphine or other strong opioid is still sometimes used first-line.[84,89]

Dexmedetomidine, a highly selective alpha$_2$ adrenergic agonist used in intensive care, is now occasionally used in PCUs to achieve 'rousable sedation' (Richmond Agitation-Sedation Scale/RASS 0 to -2) particularly in dying patients with intractable pain ± delirium.[90,91] Dexmedetomidine potentiates analgesia and reduces delirium,[92] and patients are easily roused without the need for dose reduction. When given by continuous subcutaneous infusion, it is compatible with metoclopramide, midazolam and morphine (unlike propofol).

Dexmedetomidine has been approved for use in PC by the British Columbia Provincial Drug Formulary. In one patient given dexmedetomidine subcutaneously for 2 weeks, the intractable pain was much reduced and the delirium cleared. Midazolam was added in the final week of her life when deeper sedation was necessary.[93] Dexmedetomidine is thus an alternative for patients with severe refractory symptoms (particularly when associated with delirium) who wish to remain in lucid contact with those around them.

How effective is *CSD*/CDS?

Generally, clinical observation is used to assess the level of comfort using one of the many observational scales, for example, RASS.[94] A structured questionnaire about the last patient they had cared for who had received *CSD* was completed by >500 doctors and nurses in the Netherlands working in various settings.[95] A 'favourable' outcome was associated with (i) a clear primary indication, (ii) a shorter time to achieve adequate sedation and (iii) a shorter survival time. Doctors reported 30% of outcomes as 'favourable' compared with 19% for nurses. The nurses tended to record a less favourable outcome in those who were able to continue to take food or fluid.

Furthermore, advice from a PC Home Care Team does not necessarily guarantee that CDS will be always be straightforward; families find it distressing if deep sedation is not rapidly achieved (e.g. in less than 1–2 h), and if their loved one awakes several times after initial successful deep sedation.[96]

In a prospective observational efficacy study in 21 PCUs in Japan (n = 102), CDS was defined as '*almost or complete* drug-induced unconsciousness until death'.[81] Sedation was achieved with midazolam and/or phenobarbital. Symptom relief was achieved in 83% of cases; details about the remaining 17% were not given.

Median time to achieve CDS was about 1 h (mean = nearly 5 h), but in those given phenobarbital alone, the median was 3 h. Seven percent of patients were still capable of 'explicit communication' 4 h after starting sedation. Nearly 50% of the patients awoke once after being in 'a deeply sedated state'.

In a smaller study of general practitioners in Belgium (n = 28), a similar proportion awoke after CDS had been started. In over half the patients, pain was the main indication for CDS.[97] Given that pain is commonly stated to be only a rare or non-existent indication for CDS,[61] these figures strongly support the view that CDS should not implemented without the involvement of a multiprofessional PC team.[45] When a PC Home Care Team is involved, pain is only rarely remembered by relatives as a problem in the last hours of their loved one's dying.[98]

In a study of 106 patients in nine hospices and PCUs in the Netherlands, the Discomfort Scale–Dementia Alzheimer Type (DS–DAT) was used to standardize assessments.[99] This has nine items, reflects normal clinical practice and has acceptable face validity for use in relation to sedation. CDS was associated with increased levels of comfort. However, some patients showed evidence of increased discomfort in the last hours before death, notably those who had had refractory vomiting or multiple refractory symptoms. The median duration of CDS was around 25 h, with a range from 2 to 161, that is, almost a week.

Unresponsiveness *versus* unawareness

When CDS renders someone unresponsive, it is generally assumed that the suffering has been relieved, particularly if the patient looks peaceful. However, unresponsiveness does not necessarily mean absence of awareness (unconsciousness).[100] Subjective experiences during general anaesthesia have been reported by almost 60% patients despite being unresponsive.[101,102] Similar findings have been reported from Intensive Care Units.[103] In patients diagnosed clinically as being in a 'vegetative state', over 40% demonstrate evidence of awareness with more sophisticated behavioural examination.[104]

Bispectral index (BIS) monitoring, a non-invasive means of measuring sedation,[105] has been used in several studies of sedated PC patients. Some with clinical readings indicating unconsciousness on either the Ramsey Sedation Scale or RASS had BIS readings suggesting continued awareness.[106–108] However, because signal quality and muscle activity are both potential significant confounders, there is need for caution in interpreting the readings.

Even so, the fact that it is *not* possible to equate clinical unresponsiveness with unawareness is cause for concern. Given the fact that delirium is

Table 6. Comparison of CDS and euthanasia for refractory intolerable suffering.[13,41].

	CDS	Euthanasia
Prognosis	Hours–days ('Imminently dying')	In Belgium and the Netherlands, no need to be terminally ill but 'no prospect of relief'; other statutes imply advanced progressive disease or less than 12 months
Intention	Relief of suffering	Ending life
Method	Reducing awareness	Killing the patient
Procedure	Continuous infusion of IV/SC sedatives (±dose titration)	Lethal cocktail (deliberate overdose)
Criterion of success	Relief of distress	Death of the patient
Time-scale	Hours–days (not predetermined)	Immediate death

CDS: continuous sedation until death; IV: intravenous; SC: subcutaneous.

often the primary reason for CDS, could some patients rendered unresponsive with midazolam (but with little or no antipsychotic) still be aware? The answer has to be yes. Likewise, could some patients with refractory pain rendered unresponsive with midazolam still experience severe pain? The answer has to be yes. Thus, it is not unreasonable to suggest that CDS with midazolam alone could lead to a drug-induced 'locked-in' syndrome – still delirious, still in severe pain, but unable to indicate this to one's carers.

Certainly, until the situation is clarified by further research, it is crucial to continue appropriate symptom control measures, particularly for delirium and pain, when starting CDS:

> Throughout a 40 year career in palliative care, I have never ordered 'palliative sedation' … The very concept fails to capture my clinical reasoning. I do not manage delirium, shortness of breath and pain with standard treatments and then designate a symptom 'intractable', turning to 'last resort' therapy for severe cases. I do not shift my clinical goal from symptom relief to 'sedation', nor do I pre-determine that unconsciousness is the only means by which symptoms can be relieved. (PC doctor)[57]

That said, doubtless some of his patients would have become sedated as a secondary effect from the escalation of specific symptom control measures, and possibly deeply at times.

CDS *versus* euthanasia

Conceptually, it is possible to distinguish between CDS until death and euthanasia (Table 6).[13,41] However, in practice, the boundaries can become blurred. Furthermore, if the patient is not imminently dying, CDS is tantamount to 'slow euthanasia'.

In Belgium and the Netherlands, rapid induction of deep sedation is the norm.[37] In fact, CDS is sometimes organized like euthanasia, with a family farewell before the patient is sedated:

> He was ready to go, he was physically finished. He had been able to say goodbye to everyone properly … It took him a week to get up the courage to do it … And on the day the sedation started, he again said goodbye to his children and grandchildren … and the doctor then gave him [midazolam], and he fell asleep very quickly. And we immediately attached the pump … and he didn't wake up again. (Belgian nurse)[37]

Sometimes doctors actively encourage patients to opt for CDS rather than euthanasia,[109] because it is associated with less bureaucracy (Table 7):

> She felt like, this is too much for me to bear … But it was right before Easter weekend, and for practical reasons euthanasia is not performed at the weekend … we decided with the doctor to move to sedation. (PCU nurse)[110]

> [For euthanasia] a physician should consult with the nursing team and with the family, whereas for PS

Table 7. Selected regulatory requirements for CDS and euthanasia in the Netherlands.

	CDS	Euthanasia
Prognosis	<2 weeks	No limitation[a]
'Cooling off' period	No	Yes
Second opinion	No	Yes
Paperwork	No	Yes

CDS: continuous deep sedation.
[a]The patient must be suffering unbearably without any prospect of improvement.

> there are no procedures … the profile of very dominant and hierarchical physicians matches very well with PS, because there they hold absolute sway … So it is true that there is a certain kind of physician who chooses not to perform euthanasia, but performs PS instead … 'We will quietly increase the dose' … We call those patients 'sans papier'. (Home care nurse)[38]

Summary and conclusion

The dissonance between guidelines and practice is an ongoing matter of concern.[15] Guidelines emphasize that CDS is an ethically exceptional last resort treatment for use only after standard palliative care measures have proved inadequate, and that initiation should be proportionate and progressive. However, despite low level use in some PCUs (<3%),[44,56] others report an incidence as high as 15%.[52] Nation-wide studies indicate that its use is increasing in many countries (sometimes dramatically), often implemented by non-PC specialists and family practitioners, not in conjunction with a PC Service,[51] and dose titration is often *not* the norm.[36] Furthermore, there are indisputable reports of CDS which can be described only as non-voluntary (unrequested) euthanasia.[111]

Other examples of the tendency to widen the scope for CDS include the change in the Norwegian Medical Association guidelines from 'palliative sedation for the dying' (prognosis of <2 weeks) to 'palliative sedation at the end of life' (prognosis unstated).[58] It has also been proposed that the 'last resort' criterion should be dropped, and CDS allowed for any patient with a prognosis of under 6 months.[112] Furthermore, during the Senate debates in France, it became clear that many Senators considered establishing the legal right to CDS as the first step to the decriminalization of physician-assisted suicide and euthanasia, making the present Law a type of 'Trojan Horse'.[113]

Other major ongoing concerns about CDS relate to:

1. Its use for solely psycho-existential reasons.[70]
2. Its life-shortening effect.[14]
3. The potential life-shortening effect of withdrawing or withholding CAH.
4. Its ethical distinction from euthanasia.[14,114]

To this should be added a triad of inter-related concerns:

1. Under-diagnosis of delirium, leading to
2. Underuse of psychotropic drugs, and
3. Exacerbating delirium by using midazolam alone.[62]

In addition, many clinicians are unaware that unresponsiveness does not necessarily mean unawareness.[106] Consequently, midazolam alone in patients with delirium and/or severe refractory pain could result in a drug-induced 'locked-in' syndrome, and the patient dying in great, but unrecognized, distress.[100,104]

Concern has also been expressed that the increasing use of CDS has had a negative impact on PC by unwittingly creating a culture in which all struggle is seen as unbearable suffering, and unresponsiveness equated with peace.[15,16] As one doctor said, 'The advantage of PS is that it provides an easy resolution of severe discomfort and refractory symptoms'.[77] Easy for whom? More likely for the doctors than the patients: it is much easier to increase the dose of midazolam than it is to wrestle with the issues underlying a patient's distress.[115] The focus becomes therapy rather than care, the physical dimension rather than the whole person and the primacy of intervention rather than 'receptiveness and presence'.[15] In other words, a retreat from a holistic approach into a biomedical one.

Finally, in addition to abandoning the term 'palliative sedation', it is crucial that primary (predetermined, intentional) CDS continues to be regarded as an exceptional last resort measure, rarely necessary, and ideally not implemented without the involvement of a multiprofessional PC team. The comment by an American Pediatric Pain and Palliative Care specialist is apposite:

> Only if all approaches [non-drug, drug, and anaesthetic-neurosurgical] have been exhausted concurrently, and not earlier, would it be necessary to consider sedation to unconsciousness, hence making the latter a very rarely needed intervention, estimated less than once per year in large pediatric cancer programs.[116]

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