Continuous deep sedation in patients nearing death

Imprecise taxonomy makes interpreting trends difficult

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RESEARCH, p 810

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Deep sedation is occasionally the only effective treatment for refractory symptoms and suffering in terminally ill patients. In their accompanying study, Rietjens and colleagues report a significant rise in continuous deep sedation in the Netherlands from 5.6% in 2001 to 7.1% in 2005, while cases of euthanasia declined over the same period.[1]

Continuous deep sedation is an accepted treatment in the Netherlands for patients whose life expectancy is two weeks or less. The Dutch study reports that 1200 fewer people died as a result of euthanasia but 1800 more died as a result of terminal sedation in 2005 than in 2001. Although the increase follows the publication in 2002 of guidelines for general practitioners on the use of continuous deep sedation, and attention in the Dutch media, the cause of this trend is unclear. There is concern that continuous deep sedation may enable doctors to evade the procedural requirements for euthanasia. In the Dutch study, 9% of deaths during continuous sedation were preceded by a euthanasia request from the patient that was not granted,[1] and last year 43% non-compliance with the Dutch prescribing guidelines for terminal sedation was reported.[2]

Few data are available on the frequency of these practices in the United States or United Kingdom because no comparable national population based studies have been carried out. However, sedation for the treatment of otherwise intractable symptoms has become accepted practice among US and UK clinicians treating patients with advanced incurable illnesses who are close to death. Controversy and resistance to the procedure have declined as concerns have been formally discussed, guidelines have been developed, and position statements of professional associations have been published.[3 4]

Because this treatment has become accepted in American hospice and palliative care practice, there is legitimate concern that sedation should not become a substitute for meticulous assessment and intensive treatment of physical symptoms and psychological or spiritual distress. Specialist palliative care teams regularly help patients with previously intractable pain, delirium, anxiety, or dyspnoea become comfortable. Palliative care is personalised and costly, while sedation is a relatively inexpensive, one size fits all treatment.

In 2007, international palliative care experts concluded that sedation is a valid option when other treatments fail to relieve symptoms in a patient expected to die within hours or days.[5] The panel advocated small initial doses of a short acting benzodiazepine (midazolam), which are then titrated carefully against symptoms, allowing the patient to communicate intermittently. The panel also recommended that advice from palliative care specialists should be sought before instituting sedation. Only 9% of Dutch general practitioners in this study, which was completed before this recommendation was published, had done so.

The Dutch series is important in monitoring national trends and patterns of continuous deep sedation in one country. What lessons are applicable internationally? Meaningful interpretation of these findings is impeded not only by the legality and acceptance of euthanasia in the Netherlands, but more so by a persistent deficit of clearly defined taxonomy for component treatments and practices. The term "continuous deep sedation" is not precise enough to discern the reasoning and motives of clinicians needed to support relevant ethical analyses. Euthanasia implies the intention to hasten death. If the terms "palliative sedation" and its subcategory, "terminal sedation," are clearly defined they can contribute to a meaningful taxonomy.

"Palliative sedation" applies to treatment of pain or other physical distress with sedating drugs when other approaches have failed. In critical care units, palliative sedation may be used for a prolonged period until other treatments alleviate distress or the patient deteriorates, and it is used in other settings as short term crisis management. Although patients may die during palliative sedation, it is not the intended treatment goal. "Terminal sedation" refers to palliative sedation prescribed for symptomatic patients who are expected to die soon. It is usually applied in situations in which life prolonging treatments have been stopped. Use of artificial hydration should be considered on its own merit in relation to symptom control. Death is the anticipated outcome, and titrated terminal sedation is given with the aim of ensuring that patients are comfortable as their disease causes death.

This Dutch study provides some insight into end of life management of patients with intractable suffering. We suggest that subsequent surveys that ask doctors about reported deaths use clear categories that can help us interpret empirical patterns of end of life care. Such surveys should also collect other pertinent information about treatment, such as concurrent use of medically administered nutrition and hydration, the drugs and doses given, and the interval between administration of sedating drugs and death. This would enhance our ability to compare trends related to these important components of end of life care from one country to

another over time. Further research must incorporate the perspectives of patients and families, as well as professionals from health care, spiritual care, social services and the social sciences, law, and ethics.

Clinicians and the societies they serve would benefit from informed public discourse about ethical and effective ways to alleviate persistent suffering at the end of life.

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Cardiopulmonary resuscitation for out of hospital cardiac arrest

American Heart Association advocates chest compression without ventilation

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Is ventilation of the lungs necessary when starting cardiopulmonary resuscitation (CPR) for out of hospital cardiac arrest? Increasing evidence shows that it has no effect on outcome and may even make matters worse. The American Heart Association has responded to this controversy by publishing a statement "Hands-only (compression-only) CPR: a call to action for bystander response to adults who experience out-of-hospital sudden cardiac arrest."[1] The main message of this statement is that by encouraging bystanders to provide at least chest compressions, the odds of survival from out of hospital cardiac arrest will be improved.

Several animal studies show no survival benefit with the addition of ventilation during cardiopulmonary resuscitation.[1] A limitation of these studies, however, is that the airways of the animals are generally patent, which may enable chest compressions alone to generate some ventilation, particularly if gasping also occurs during chest compressions. Unconscious supine humans usually have an obstructed airway, and gasping occurs less often than in the animal models. In a recent Japanese study, only 7.1% of patients with out of hospital cardiac arrest were gasping when ambulance personnel arrived on the scene.[2] Severe hypoxaemia developed rapidly in a compression-only cardiopulmonary resuscitation animal model with an obstructed airway.[3]

Surveys indicate that bystanders and medical professionals are reluctant to do mouth to mouth ventilation (rescue breathing), partly because of fears of infection, but also because it is considered unpleasant.[4-6] Contrary to these findings, lay people trained in basic life support, who were interviewed after witnessing cardiac arrests but who did not perform bystander cardiopulmonary resuscitation, indicated that this was mainly because of panic; only four out of 279 (1.4%) of them said that it was because they objected to doing mouth to mouth ventilation.[7] Compression-only cardiopulmonary resuscitation is easier to learn than conventional resuscitation.[8] Lay people cannot follow telephone instructions from ambulance dispatchers to give mouth to mouth ventilation and chest compressions while waiting for an ambulance to arrive. In a study of dispatch assisted (telephone) cardiopulmonary resuscitation, instructions were more likely to be followed when the ventilation component was omitted, and survival was similar in the compression-only group.[9]

Several observational studies show similar survival rates when bystanders use compression-only cardiopulmonary resuscitation or conventional resuscitation.[1] Most importantly, all these studies show that any method of cardiopulmonary resuscitation increases survival compared with no resuscitation. Although compression-only cardiopulmonary resuscitation is not associated with statistically better survival overall compared with conventional cardiopulmonary resuscitation, one of these studies reported that outcome was significantly better for the compression-only group when response times were short.[2] When the time from collapse to first attempt at resuscitation by a bystander was four minutes or less, a favourable neurological outcome was achieved in 10% (23/227) of the compression-only group compared with 5% (18/351) of the conventional cardiopulmonary resuscitation group (odds ratio 2.1, 95% confidence interval 1.1 to 4.0). The most recent studies have been accompanied by a plea for an urgent change in cardiopulmonary resuscitation guidelines.[10]

Should we teach lay people to perform compression-only cardiopulmonary resuscitation? In the United Kingdom each year, bystander cardiopulmonary resuscitation occurs in a third of the roughly 30 000 ambulance treated cardiac arrests (figures based on unpublished Ambulance Service Association and Joint Royal Colleges Ambulance Liaison Committee data). The logic behind promoting compression-only cardiopulmonary resuscitation is that it increases the frequency of bystander cardiopulmonary resuscitation, and that any bystander cardiopulmonary resuscitation will increase the chance of long term survival compared with no resuscitation. This should benefit victims of out of hospital cardiac arrest from a cardiac cause when ambulance response times are short. Most (65-80%) out of hospital treated cardiac arrests have a primary cardiac cause.[2 11] The potential losers of a compression-only cardiopulmonary resuscitation approach are people who are likely to benefit from both ventilation and compressions, such as people having arrests that are associated with drowning, trauma, or airway obstruction;

those having primary respiratory arrest or prolonged cardiac arrest; and children having cardiac arrests. People who favour compression-only resuscitation argue that these groups have a low survival rate even with conventional cardiopulmonary resuscitation, and a change to compression-only cardiopulmonary resuscitation will have an overall benefit by increasing the number of survivors from primary cardiac arrest.

The American Heart Association statement indicates that compression-only cardiopulmonary resuscitation does not apply to unwitnessed cardiac arrest, cardiac arrest in children, or cardiac arrest presumed to have a non-cardiac cause. This implies that lay people must be able to differentiate a primary cardiac arrest from cardiac arrest from a non-cardiac cause and would need to be trained in conventional cardiopulmonary resuscitation as well as compression-only resuscitation. We do not know whether lay people can distinguish between primary cardiac arrest and primary respiratory arrest. If guidelines for lay people are changed to compression-only cardiopulmonary resuscitation for witnessed sudden collapse, should we continue to teach mouth to mouth ventilation for primary respiratory arrest?

The evidence for and against the use of compression-only cardiopulmonary resuscitation instead of conventional resuscitation (30 compressions and two ventilations, repeated until help arrives) is being fully evaluated, along with a wide range of other resuscitation topics, in preparation for the 2010 Consensus Conference on Cardiopulmonary Resuscitation Science. After this conference, international resuscitation guidelines will be revised and implemented.

For the time being, in line with the current European and UK guidelines,[12] lay rescuers who are not trained in cardiopulmonary resuscitation, or those not willing or unable to give effective mouth to mouth ventilations, should give compression-only cardiopulmonary resuscitation at a rate of 100/minute. Those rescuers who are trained in conventional cardiopulmonary resuscitation should ensure that ventilations and any other interventions cause only minimal interruption of chest compressions.

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Universal *RHD* genotyping in fetuses

Is effective, and could dramatically reduce unnecessary anti-RhD prophylaxis

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RESEARCH, p 816

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Non-invasive detection of fetal *RHD* status using maternal plasma is one of the few real advances in fetal medicine or obstetrics in recent years. DNA amplification of one or more region of the *RHD* gene can predict the fetal genotype with an accuracy of almost 99%.[1 2] This means that invasive procedures (amniocentesis and chorionic villus sampling)—which carry a small but important risk of pregnancy loss and may also increase the risk of sensitisation in pregnancies at risk from fetal haemolytic disease—can be abandoned.

Non-invasive ascertainment of the fetal *RHD* genotype (and other red cell antigens) is now used routinely in the United Kingdom and elsewhere in the world.[3] The technology, although labour intensive, is relatively simple and very reliable. In the accompanying study, Finning and colleagues assess the feasibility of applying a high throughput method for predicting RhD phenotype from fetal DNA in the plasma of pregnant women who are RhD negative.[4]

The incidence of *RHD* alloimmunisation has fallen greatly since the introduction of anti-RhD prophylaxis. In the 1960s prophylaxis was given in the postpartum period, and more recently after sensitising events and during the antenatal period. Antenatal prophylaxis is now offered to all *RHD* negative women in the UK and most developed countries regardless of the fetal genotype. But this approach has problems. Anti-D immunoglobulin is produced from pooled plasma taken from *RHD* negative male donors who have been injected with RhD positive red cells. Although the plasma is purified, the risk of infection remains. Outbreaks of hepatitis C have occurred, but with modern techniques the risk is minimal, although the possibility of infection with a viral or prion agent remains. Anti-RhD immunoglobulin is also in short supply and expensive, and the logistics of giving one or two doses antenatally is labour intensive and expensive. These injections are also painful and inconvenient, and many mothers have difficulty in accepting their need, especially as they are given without regard for fetal *RHD* status.

Currently, non-invasive fetal *RHD* genotyping is usually available only to women who have been sensitised—indicated by the detection of anti-D antibodies in an antenatal sample. After confirmation of the fetal genotype, only women carrying an *RHD* positive fetus are monitored for signs of fetal anaemia. Women with an *RHD* negative fetus can be discharged to routine obstetric care.

In their prospective study, Finning and colleagues assess high throughput *RHD* genotyping of fetal DNA in maternal plasma at 28 weeks—just before the first dose of antenatal anti-D injection—in about 1800 *RHD* negative women. The correct fetal genotype was predicted in almost 96% of cases, with a small false negative rate of 0.16%. The results were either inconclusive or unobtainable in only 3.4% of cases. These findings are important for two reasons. Firstly, they demonstrate the reliability of the automated technique and the feasibility of large scale antenatal testing. Secondly, if this approach was used for all *RHD* negative women, only 2% of these women would receive unnecessary anti-D prophylaxis, compared with 38% using the current system. This is a substantial reduction of an antenatal intervention.

The benefits of wider implementation of antenatal fetal genotyping are obvious. Antenatal prophylaxis can be given to those women who actually need it. The need for anti-RhD prophylaxis after potential sensitising events can also be eliminated if the fetus is definitely not at risk. This approach may also have financial implications. Although Finning and colleagues' study did not assess costs, mass testing would probably reduce costs. The costs of testing everyone need to be balanced against the costs of giving immunoglobulin to everyone, but again mass testing is likely to result in a net saving by reducing pharmacy and manpower costs.

The consequences of a false negative result are important because withholding prophylaxis could potentially result in alloimmunisation and put the fetus and subsequent pregnancies at risk of haemolytic disease. In this study, only three samples (0.16%) gave false negative results. However, these samples were analysed more than 14 days from collection because of problems with transport. This delay would reduce the accuracy of the results because the amount of maternal DNA relative to fetal DNA increases in older samples, probably as a result of lysis of maternal cells in the specimen. The authors point out that under normal laboratory testing criteria these samples would have been discarded.

The consequences of a false positive result are far less detrimental. Some women will receive unnecessary anti-RhD prophylaxis as they do now, but the numbers would be small. Strict adherence to protocol would minimise the risks of false negative, false positive, or inconclusive results.

Although this study looked at samples taken from women at 28 weeks' gestation, many potentially sensitising events occur before this time. If fetal genotyping is performed only in the third trimester many women will still receive unnecessary anti-RhD prophylaxis. Furthermore, prophylaxis after invasive first or early second trimester procedures will still be required. The goal of non-invasive testing is to determine fetal genotype as early in pregnancy as possible. Earlier gestation feasibility studies are in progress.

Universal fetal genotyping of all *RHD* negative women is the logical extension of a service that is already readily available. Automated techniques should make mass testing easier and cost effective, and they should minimise the risks of receiving an unnecessary blood product. If these techniques are shown to be as reliable earlier in pregnancy the arguments for recommending universal testing will be compelling.

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Oral bisphosphonates and atrial fibrillation

The risk is negligible, and does not offset the benefits of reducing fractures

RESEARCH, p 813

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The benefits of bisphosphonates for the prevention of fracture in patients with osteoporosis are not disputed,[1 2] and one trial has also reported reduced mortality in these patients.[3] Nevertheless, bisphosphonates are underused by those most likely to benefit—elderly patients with fractures.[2] This shortfall in care was difficult to rectify even while bisphosphonates were considered effective and safe,[2] but matters will probably get worse after recent reports that these drugs might increase the risk of atrial fibrillation.[3-6] Even fewer eligible patients are now likely to start taking bisphosphonates, and more treated patients are likely to stop taking them. This would be justified if the risk of atrial fibrillation were real and large enough to offset the known benefits for fracture reduction. However, this potentially increased risk is challenged by an accompanying population based observational study by Sørensen and colleagues, which finds no significant increase in atrial fibrillation or flutter in women taking bisphosphonates for osteoporosis.[7]

It was only a matter of time before osteoporosis, its treatments, and cardiovascular events were linked.[8 9] Osteoporosis is common, it affects people with an increased risk of cardiovascular disease—such as postmenopausal women and elderly people—and it has been associated with adverse cardiovascular events.[9]


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Classic risk factors for atrial fibrillation such as older age, hyperthyroidism, and smoking increase the risk of osteoporosis. Also, both osteoporosis and atrial fibrillation can be relatively clinically silent. For example, implantable event monitor studies of patients with treated atrial fibrillation find almost 40% of those with extended (>48 hours) recurrences are completely asymptomatic.[10] With this scenario of at risk patients sharing similar risk factors, any secondary or post hoc analyses of osteoporosis treatments and adverse cardiovascular events will be difficult to interpret and susceptible to serious confounding and problems related to multiple comparisons.[8]

So how strong is the evidence that bisphosphonates cause atrial fibrillation? To date, four studies have reported the link between these drugs and atrial fibrillation (see table on bmj.com).[3-6] Of most concern is the horizon pivotal fracture trial,[3] which compared annual intravenous zoledronic acid with placebo in almost 7800 postmenopausal women. Over three years, new atrial fibrillation did not significantly increase (2.4% of zoledronic acid users *v* 1.9% of controls; P=0.12); however, the ill defined entity of "serious" atrial fibrillation did significantly increase (1.3% of zoledronic acid users *v* 0.5% of controls; P<0.001). The evidence available so far indicates that the absolute risk of atrial fibrillation is very small, and if present at all, it is probably associated with intravenous zoledronic acid and not the more commonly used oral agents (see table on bmj.com). A meta-analysis of individual patient data might help to define the risk of atrial fibrillation with bisphosphonates.

That said, secondary analyses from trials and meta-analyses may not constitute best evidence when dealing with rare drug related adverse event rates (<1-2%) and two common conditions that are found in the same older population. Unlike the use of non-randomised studies to estimate treatment effects without a trial (as used for oestrogen and heart attack) or to find wholly unexpected benefits (as used for statins and prevention of sepsis or cancer), a large and well conducted observational study is perhaps better suited to determining unexpected harm from commonly used drugs.[11]

Sørenson and colleagues report such a study.[7] They investigated disodium etidronate and alendronate in a Danish population based nested case-control study (around 14 000 cases of atrial fibrillation and around 68 000 controls) conducted from 1999 to 2005. The timing of their study is important because prescribers would have had no concerns about any risk of atrial fibrillation, which otherwise might have introduced confounding by prognosis.[11] In terms of databases and methods used, the study is rigorous and adequately powered. The investigators report almost no difference in the use of bisphosphonates in people with atrial fibrillation and those without (3.2% of current users had atrial fibrillation *v* 2.9% of non-users). No association was seen in appropriately adjusted analyses that examined new users versus not new users (the least biased comparison), former users versus not former users, and long duration versus short duration of use. To replicate "serious atrial fibrillation" as reported in trials (see table on bmj.com), Sørenson and colleagues also restricted analyses to events needing hospital admission or cardioversion, and again they found no clinically important associations.

The main limitation of their work is lack of information about zoledronic acid. This is important. Previous reports[5 6] and Sørenson and colleagues' work[7] suggest that oral bisphosphonates are safe with respect to atrial fibrillation. But atrial fibrillation might possibly be triggered soon after an infusion with zoledronic acid (or other intravenous bisphosphonates) as a result of the release of proinflammatory cytokines or transient hypocalcaemia and secondary hyperparathyroidism.[5 7] However, in the HORIZON pivotal fracture trial, most cases of atrial fibrillation occurred months after infusion, and electrocardiograms done in 559 patients before and nine to 11 days after infusion did not differ with respect to the presence of arrhythmias, which suggests that neither of these possible mechanisms was responsible.[3] Nevertheless, the makers of zoledronic acid should do their utmost to confirm or allay concern, by pooling individual patient data and conducting postmarketing surveillance studies.

What are the implications for clinicians who commonly and appropriately prescribe oral bisphosphonates for their older patients with fractures and osteoporosis? For now, beyond taking the patient's pulse and ordering an electrocardiogram when it is irregular,[12] available evidence suggests that business should carry on as usual—the risk of atrial fibrillation associated with oral bisphosphonates seems to be vanishingly small if it exists at all, and it is unlikely to ever offset the confirmed benefits of these drugs in the prevention of fractures.

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Selecting medical students

Tests of cognitive ability are probably the best method at present

FOTOLIA

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The selection of the doctors of tomorrow is a subject of constant interest because it raises questions about ensuring equity, predicting human behaviour, and defining the characteristics of a good doctor. In the United Kingdom, it costs about £200 000 (€260 000; $400 000) to train each medical student, but the cost of getting the selection wrong is much greater.

Selection takes place under considerable time pressure—in the UK around 19 000 applicants must be screened for some 8000 places in less than six months, and each applicant may apply to four medical schools. The selection ratio in the United States is remarkably similar—around 42% of 42 000 applicants were successful in 2007, although each student made an average of 13 applications.

Different specialties have different requirements, but from our reading of the literature we distil three broad attributes that doctors should have—cognitive ability (including linguistic and mathematical intelligence, problem solving capacity and memory); humanity (kindness, empathy, emotional intelligence, bedside manner and ability to work in a team); and diligence (care in clinical practice, capacity to work hard, punctuality, honesty and conscientiousness). Although the best option would be to screen potential doctors for all these attributes, the evidence suggests that only cognitive ability can be assessed with reasonable accuracy by a mass selection process. School examination results have been shown to predict academic performance at medical school.[1] However, it has been argued that British A levels are not useful because most candidates applying for medical school achieve the top grades and also not fair because they favour students from more privileged backgrounds. These criticisms could be rectified by basing selection on actual marks awarded rather than course grades on an A-E scale and adjusting entry requirements according to the applicant's background.

Despite these potential solutions, some medical schools have introduced aptitude tests, based mainly on cognitive tasks. Some tests, such as the biomedical admissions test, correlate well with preclinical examination results,[2] whereas others, such as the graduate Australian medical school admissions test, are less predictive.[3] These aptitude tests do not seem to predict clinical performance,[3 4] so they may have little value as independent predictors of performance beyond medical school. Furthermore, aptitude tests are costly for candidates and universities and do not seem to improve prediction over public examination marks alone.

Can psychological tests be used in selection? Personality influences career progression and job satisfaction; doctors who score highly for introversion and neuroticism make relatively heavy weather of their professional lives.[5] These same traits, however, may also predispose doctors towards safe and careful clinical behaviour.[6] We simply do not know the mixture of traits that is most predictive of both diligent service and personal progression.

Tests to measure "empathy" are not useful for selection because the results vary over time and such tests are poor predictors of clinical performance.[7] In addition, unlike IQ scores or examination results, psychological tests can be manipulated to provide socially desirable answers. Questions designed to spot "faking" are far from foolproof,[8] and it would be unfair to exclude students on the basis of alleged gaming.

In the meantime, we are left with another relatively unstudied process: the short medical student interview. Interviews promise much and can be an effective recruitment tool, but their predictive accuracy is low.[9] Agreement among interviewers is slightly greater at the extremes of the rating scale, so interviews could help eliminate extreme phenotypes.[10] Even in these cases, however, interviews let through people they are meant to eliminate,[11] and they may be biased towards people with a pleasing appearance. Interviews have been described as "a very elaborate, labour intensive and expensive lottery,"[12] and we recommend that they are used only in the context of research, to test whether improvements to the interview process can predict a desirable behaviour downstream.

As interviews and psychological tests seem unable to select for desired attributes, we think that tests of cognitive ability are the best option for the present. We favour examination percentage scores over IQ scores or aptitude tests because the cognitive processes they test are similar to those used in clinical practice—the application of knowledge to a problem.

Clever people are not known to be systematically less humane than others.[12] So, in selecting students we might as well test for the one attribute for which valid methods of prediction exist—cognitive ability—while using the opportunity to "test the test" and add to the currently sparse evidence base.[4] For example, the proposed pilot schemes for specialty selection in the English Modernising Medical Careers programme will be evaluated prospectively. Many countries in continental Europe use random selection, with each student's chances weighted by school leaving examination results. While we would rather rely on examination marks alone, such a "weighted lottery" at least avoids the illusion of scientific probity inherent in psychological tests or interviews.

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