Prescribing at Times of Clinical Transition in Chronic or Progressive Diseases

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SUMMARY

The goals of all clinical care are based on optimizing a person's comfort and function in physical, emotional, existential, sexual and social domains. Chronic, progressive illnesses generate specific challenges as systemic deterioration shifts the benefit–toxicity balance for the treatment of some long-term comorbid diseases. At every clinical encounter, and especially at times of transition in clinical care (admission to hospital, discharge to the community, a new diagnosis), the opportunity to review the management of comorbid conditions must be taken. This is especially important when a life-limiting illness is first recognized. Careful rationalization of the treatment of chronic comorbid conditions in a systematic way as a person experiences systemic deterioration requires a framework for considering short- and long-term sequelae of both treating and not treating a given condition. The preventative intent of therapy (primary, secondary, tertiary) must be known to make this clinical decision. The numbers needed to treat to avoid one adverse outcome will tend to increase as a person experiences systemic decline and, conversely, the numbers needed to harm will decrease. In addition to reviewing individual medications, consideration must be given to the total burden of prescribing for cumulative effects (e.g., risk of drug–drug interactions, anticholinergic load). Judicious dose reduction or substitution of a more appropriate agent, given the global decline, with continued careful review will allow medications to be titrated to minimize harm at the end of life. [International Journal of Gerontology 2009; 3(1): 1–8]

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Introduction

There is a need to define the goals of clinical care and how the theory of such care is matched by the health system and those working in it. The goals of clinical care may seem self-evident, but it is only self-evident if actions are directly matched to the best available evidence for practice. Such considerations are especially important at times of clinical transition, such as presentation to the emergency department, admission to intensive care or discharge from an inpatient unit to the community for the frail, those with complex and multiple comorbidities, and those with life-limiting illnesses. How can clinicians minimize iatrogenic harm expectantly?

What are the Goals of Clinical Care?

In the early 1980s, Dr Eric Cassell wrote a seminal article in the *New England Journal of Medicine* presenting a very strong case that the key role in clinical care was the relief of suffering[1]. The underlying need for Cassell

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to write the article was the perception that clinical practice had or is at risk of moving away from this fundamental focus valued by patients, their families, and the broader community. Reflection on current practice suggests that, at times, clinicians still replace patient-centered care with clinician-directed care without always considering the individual person in his/her current circumstance.

One can further characterize the goals of care in terms of optimizing function, i.e., physical function, emotional function, existential or spiritual function, social function, sexual function, and financial function. Even this construct may not be sufficient to focus a wide range of health practitioners providing care in disparate settings to an individual. McCaffery et al.[2], in a letter to the *Journal of Pain and Symptom Management*, have characterized the patient's focus even more succinctly: "Are you able to do the things that are important to you?". The goals of care, therefore, become optimizing factors reflected by people with life-limiting illnesses and their caregivers, such as the function and comfort in each of the domains that are of significance to the patient and that define the breadth of personhood[3,4].

Miles Little, an hepatobiliary surgeon, challenges clinicians in his book *Humane Medicine*, proposing seven archetypal consultation types defined by whether there are signs or symptoms, whether quality of life or autonomy is threatened, and whether there are demonstrable biomechanical abnormalities[5]. Clinical care is very good for the treatment of acute medical, surgical, obstetric and traumatic emergencies; however, one could argue that clinical care responds poorly to someone with back pain with no objective signs or symptoms, whose quality of life may be greatly impaired but has no demonstrable biomechanical abnormalities on imaging or pathologic testing. As such, when we think about goals of care, we need to be aware of the very great limitations in clinical practice that exist and will continue to exist.

Optimizing physical function requires objective measurement. The Australian-modified Karnofsky Performance Status (AKPS) scale (100 indicates well, and 0 indicates dead) correlates with prognosis as it changes towards the end of life[6]. It also helps to predict the need for additional supports; a Karnofsky of 70 is the point at which people start to need additional physical support.

The goals of care are focused around the person with a life-limiting illness, defined in optimizing a number of domains, all of which need to be measured objectively if clinical care is going to realize the opportunities for improving outcomes for each individual person who comes in contact with health services.

Times of Transition—An Opportunity to Reassess Health, Function and the Aims of Care

Any interaction with health professionals should be an opportunity for patients to revisit the fundamental goals of care. This is especially so for people whose functional status is starting to become impaired, and whose vulnerability to iatrogenic harm is greater. A person starting to need additional care as their Karnofsky falls below 70 is typically an older member of the community with increasing numbers of comorbid problems, medications for these conditions, and frailty with a reduced ability to respond physiologically to rapid changes in homeostasis (Figure 1).

In resource-rich countries, about 50% of people will have warning of their deaths. Perversely, given our improved health status translating into enhanced life expectancy, the more likely we are to suffer from chronic, progressive diseases and, therefore, have warning of our deaths. The majority of people are now dying from progressive deterioration and chronic complex illnesses rather than acute events in otherwise well people. Such illnesses now include cancer, end-stage organ failure, neurodegenerative diseases, and AIDS.

The typical trajectories of functional decline have been codified into three major archetypal patterns: progressive frailty, end-stage organ failure, and cancer[7]. Frailty delivers a progressive decline in function with no sudden changes. End-stage organ failure is characterized by an overall decline punctuated at times by acute-on-chronic deterioration (a saw-tooth pattern), when recovery from each acute deterioration fails to achieve the previous level of function before the episode of decompensation. The trajectory of cancer is one of gradual decline with a precipitous acceleration in decline in the last weeks or months of life.

Such predictable deterioration leads to a concept of a "final common pathway". Anorexia, weight loss and fatigue in advanced diseases are the systemic manifestations of the body's attempt to maintain homeostasis. Unless the underlying cause can be reversed once cachexia, with its inherent loss of lean body mass and

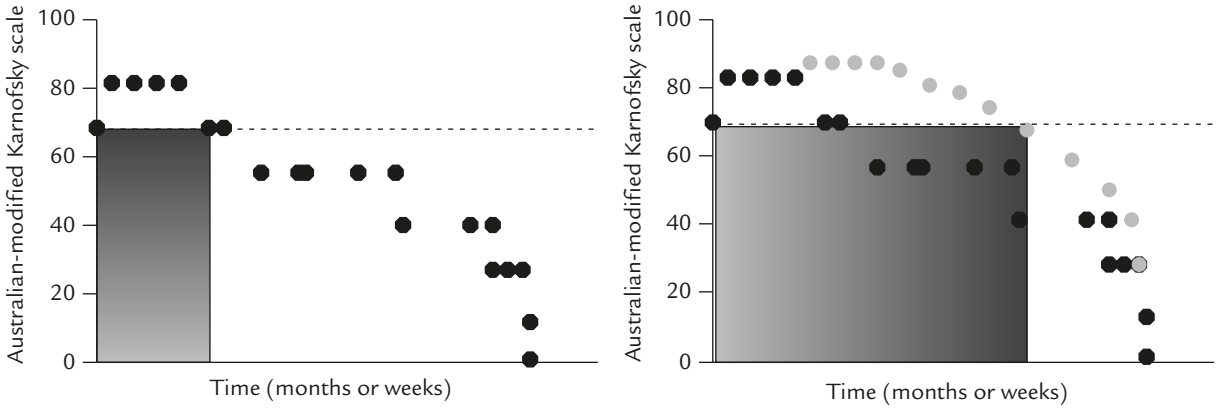

Figure 1. Better maintenance of functional physical independence for people experiencing a predictable decline in function as part of a progressive illness by increasing the amount of time a person has an Australian-modified Karnofsky Status scale score of > 70 (dotted line) with identical prognoses.

catabolic destruction of muscle is established, the person's prognosis is predicted by the rate of systemic decline. All three disease trajectories share these systemic changes.

As people come into contact with the health system, how effectively does the system (and those working in it) recognize: (1) the opportunity to optimize this person's function by minimizing any functional decline throughout their contact with the health service (especially as inpatients in hospital); and (2) where people are systemically on their disease trajectory? For example, in many hospitals around the world, people still do not die. Instead, they have cardiac arrests where resuscitation is unsuccessful. In such a model, death is seen as a failure or adverse outcome rather than as an inevitable outcome of systemic decline that had been carefully, though unknowingly, documented in the person's clinical notes. Indeed, most of us have been socialized through our clinical training to consider death as the ultimate professional failure, yet rarely in our health systems is death in this setting a result of medical misadventure.

In the setting of deterioration, there needs to be a distinction between futile treatment (where there are potential value judgments) and *clinically* futile treatment (where there are objective measures of outcomes given a particular course of action)[8]. Clinically futile treatment deals with objective outcomes. Such a model requires a clear understanding of predictable disease progression and the ideal response of clinicians and health systems to the person's actual needs.

The other challenge in times of transition is that every systemic insult is likely to have an irreversible component. Once a person has entered that final common pathway, where nothing is going to substantially change the course of their life-limiting illness, recovery from any acute deterioration is unlikely to return to the level of function before the insult. For many people, such deterioration can be due to poorly managed comorbid illnesses not adequately reviewed in the context of the person's systemic deterioration. As people enter the final common pathway, it is important to recognize the changes to metabolism for medications as cachexia progresses. This applies for pre-existing medications as well as medications added for symptom control. Furthermore, increasing numbers of medications raise the risk of clinically significant drug interactions and iatrogenic adverse events.

Given the three proposed trajectories of decline, and that optimizing function is the key goal of care, there is a clinical imperative to: (1) minimize insults which may precipitate an acute deterioration in overall function; and (2) make every effort early to work towards regaining the person's previous functional status when there is a sudden, reversible decline in function.

In optimizing outcomes by maintaining better function, there is the potential to prolong the period during which people have functional independence. Graphically, this could be considered as increasing the area under the curve for functional independence (time above AKPS, 70) while prognosis remains unchanged (Figure 1). This model quantifies the goal of a better maintained physical performance where the curve of functional deterioration is shifted to the right, knowing that a decline in function will predictably still occur.

A Framework for Prescribing as Functional Status Declines (Figure 2)

Almost all prescribing in chronic complex disease is built around commencing medications. Given the risks of polypharmacy and the predictable systemic decline in progressive illnesses that affects the pharmacodynamics of medications, how do we predictably and safely rationalize medications in these people?

As clinicians, are we simply waiting for side effects such as postural hypotension to present because antihypertensives have been continued despite extensive weight loss, or symptomatic hypoglycemia to emerge because glycemic agents have been continued despite major changes in oral intake and body mass? Conversely, precipitously ceasing medications may be as dangerous as continuing long-term medications for inactive comorbid conditions.

Prescribing at the end of life

Data from a large randomized controlled trial of health service delivery in palliative care had more than 460 people and their general practitioners participate from the time of referral until death. A secondary analysis of prescribing from that study demonstrated an increase in the number of medications prescribed as death approached because of the addition of medications for symptom control with few reductions in medications for comorbid illnesses[9]. For the majority of people, the total number of medications surpassed seven, increasing the estimated likelihood of drug–drug interactions to more than 80%[10].

Another analysis of the same data showed an increase in total anticholinergic load, closely mirroring the increased use of medications for symptom control (given their known anticholinergic activity). The absolute number of medications did not peak until the week before death. Given the need to focus on symptom control at this time and hence an inability to decrease these medications at the end of life, careful rationalization of medication used for comorbid diseases will minimize adverse effects and interactions with medications required for symptom control.

What are the consequences of increasing the anticholinergic load? Four levels of anticholinergic activity have been attributed to every medication: (1) no known anticholinergic activity; (2) potential anticholinergic activity; (3) clinically significant anticholinergic effects, which are sometimes seen; and (4) marked anticholinergic effects[11]. Three significant findings from multifactor analyses were noted for those with high anticholinergic load: (1) performance status was diminished by 15% over those with little or no anticholinergic load; (2) global quality of life was significantly reduced; and (3) increasing difficulty in concentration. Higher levels of anticholinergic load are directly associated with three key areas that impinge on one's ability to "do the things that are important"[2].

How can prescribing be rationalized to reduce the risk of iatrogenic harm from predictable effects of individual medications or the cumulative effects of medications causing anticholinergic load?

A discussion on managing medications for comorbid conditions as end of life approaches covers topics as diverse as hypertension, atrial fibrillation, diabetes, hormone replacement therapy, opportunistic infection prophylaxis, and immunosuppression following organ transplantation. In all these clinical settings, there is a need to work carefully with patients and their families to ensure that as goals of care are revised and new clinical targets developed, people understand the rationale behind such decision making. For example, someone with type II diabetes who has maintained careful glycemic control over many years will need to be supported as the target for glycemic control is adjusted upwards, to account for loss of appetite, irregular eating at the end of life and potential steroid use to avoid (rapidly fatal) hypoglycemia while avoiding an episode of symptomatic hyperglycemia.

Characteristics of the illness—phase of care

There is an active assessment that each clinician seeing a patient for the first or 100th time needs to do. In chronic complex or chronic progressive disease, there are recognizable phases of care. Eagar et al.[12] developed the idea of "phase" from more than 30,000 encounters between health professionals including nurses, doctors and allied health practitioners, and patients to define what now appears to be a simple and intuitive model for people as the life-limiting illness progresses. There are three phases, independent of diagnosis or prognosis, on which it is important to focus in this discussion: stable; unstable; and deteriorating. *Stable* is recognized if functional status is unchanged over a period of weeks to months. *Unstable* defines the person's clinical condition changing rapidly and unexpectedly—a key transition point. *Deteriorating* describes the changes seen in this person relating to the predictable

Characteristics of the illness	Question 1			
	What phase of illness is this person in?	Terminal, deteriorating	Unstable	Stable
	Question 2			
	What is the activity level of this comorbid illness?	Inactive	Active	
	Question 3			
	Is the comorbid illness improved by weight loss?	Yes	No	
	Question 4			
	What is the likely time to onset of any increase in disease activity if the medication is reduced?	Short	Long	
Medication characteristics	Question 5			
	Are there changes in the pharmacokinetics of the medication–absorption, volume of distribution (cachexia), metabolism or excretion (worsening renal or hepatic function)?	Yes	No	
	Question 6			
	Is there a known withdrawal syndrome from the medication?	No	Yes	
Intent of prevention	Question 7			
	What is the level of prevention being sought by the current therapy?	Primary	Secondary	Tertiary
Characteristics of risk assessment	Question 8			
	Is the number needed to treat (NNT) high?	Yes	No	
	Question 9			
	Is the number needed to harm (NNH) low?	Yes	No	
	Question 10			
	Will the NNT to avoid a single event be likely to increase with disease progression?	Yes	No	
	Question 11			
	Will the NNH to cause an adverse event decrease with disease progression?	Yes	No	
	More likely to cease medication		More likely to continue medication until further reassessment	

Figure 2. Decision-making checklist for prescribing for comorbid conditions in people with chronic complex or chronic progressive illnesses—medication reduction, cessation or substitution.

and expected trajectory of their life-limiting illness. The latter needs to be actively recognized by clinicians especially at times of transition; and if a person's presentation is not clearly an "expected" deterioration, further investigation is needed to determine the cause for the changes leading to this clinical presentation.

It is most often when people become unstable that they have contact with health services, and this is an important opportunity to consider the appropriate management and to review the overall goals of care. The more acute the change, the more likely a cause will be found. However, finding a cause does not necessarily lead to treating that cause; this requires a careful discussion with the patient in the context of his/her life and their wishes at this time.

Even with an expected deterioration, there is the question of prognostication. Five key global issues help to inform a person's prognosis: (1) the person's life-limiting illness; (2) their comorbid illness or illnesses; (3) their response to disease-modifying treatment for the life-limiting illness; (4) changes in systemic parameters (the final common pathway reflected in deteriorating functional status); and (5) the person's own view of their future.

A specific focus when someone presents with an unexpected change in their overall condition and function is for the health professional to ask whether a medication caused the presentation? If not, does any medication need to be modified to cope with the acute changes? For instance, if this person is now hypotensive, do their antihypertensive agents need to be ceased at least in the short term and then reviewed once they are stable? Is there a need for permanent reduction in their medications to reduce the risk of future similar adverse events?

Characteristics of the illness—comorbid diseases affected by weight loss

Which medications or disease states will be most affected by weight loss? Prior to the advent of antihypertensive and hypoglycemic agents, people were advised to lose weight as treatment for hypertension and diabetes. The weight loss of chronic and malignant disease appears to improve blood pressure and glycemic control. However, weight loss in the cachectic patient is predominantly muscle loss, which conversely may worsen other chronic or comorbid illnesses such as respiratory function in chronic obstructive airway disease.

Medication issues—pharmacokinetics

Every facet of pharmacokinetics can be affected by the changes experienced in progressive life-limiting illnesses. Absorption can be affected by gut transit and changes in the gut wall for orally administered medications. Volume of distribution will change with changes in relative contributions of adipose tissue and muscle. Both metabolic and excretory pathways may be affected by worsening renal or hepatic function. Dose reduction or substitution of another class of medication with the same clinical benefit but an alternate metabolic pathway may need to be considered for people who need to stay on such a medication.

Medication issues—withdrawal

There may be explicit known withdrawal syndromes that need to be carefully managed while the patient is still well enough for downward titration of medications. This is done rather than abruptly terminating them because of unacceptable side effects and further toxicity associated with acute withdrawal[13]. Such care requires careful continuous assessment of where this person is on their disease trajectory.

Likely time course for recrudescence of an inactive comorbid condition because of medication reduction or cessation

If a medication dose is reduced or the medication ceased, what is the time course to onset of symptoms or disease? Is there simply a linear relationship between time and risk, or is there a likelihood that an acceleration of the underlying disease state may shorten the time to symptom onset? Once diabetes has caused end-organ damage, the changes are irreversible, but the time course for this impairment is essentially linear for time and blood glucose levels, measured over long periods of time.

Intent of prevention

It is imperative to know the original intent of a medication being prescribed. Primary prevention seeks to avoid disease or modify risk. Secondary prevention treats an asymptomatic state, and tertiary prevention is to treat an established disease process. In these definitions of prevention, the same illness may require identical treatments for differing levels of prevention. For example, in hypertension, a person could require treatment for secondary prevention (an asymptomatic state) or an identical antihypertensive for tertiary

prevention because of evidence of end-organ damage. Therefore, it is important to consider the indication for the treatment and, thus, relevance to therapy in people with life-limiting illnesses.

Risk—numbers needed to treat or to harm

The other concept that underpins good prescribing, especially in chronic complex or chronic progressive illnesses, is the number needed to treat (NNT) (or number needed to harm [NNH]) to deliver a clinical benefit (or an adverse outcome). NNT is the inverse of the absolute risk reduction, and this allows us to compare widely varying therapies in a very simple way.

Linking NNT to prevention, the NNTs will be lower for tertiary prevention than for primary prevention for the same condition[14]. Within the context of people at the end of life, NNT can be a tool to assist with ceasing medications and, therefore, not simply commencing medications for comorbid illnesses.

NNT and NNH deal with single medications and do not consider the cumulative effects of several medications prescribed simultaneously for the same or other comorbid illnesses. There is a need to consider how to integrate concepts such as anticholinergic load and drug–drug interactions into a treatment–harm equation.

The definitions of NNT and NNH have no time courses associated with them. How many people need to be treated for what length of time to avoid one event? The number needed to treat (or harm) may not be linear. Treating 100 people for 5 years may not be the same as treating 500 people for 1 year, particularly given the onset of action of a therapy, ceiling effects or cumulative toxicity.

When time is factored into the calculation of NNT or NNH, the NNT will rise for patients whose prognosis is rapidly diminishing, and the NNH may well decrease for a set benefit. At some point, toxicity of therapy may well outweigh benefit as global function declines. The therapeutic window (crudely considered as: NNT–NNH) will narrow and may become negative for many frequently encountered comorbid illnesses that have been treated with stable doses of medication for years or decades.

For each medication prescription renewed in hospital or in the community, it is important to know the aim of therapy, i.e., what was being prevented, particularly for comorbid conditions. This framework is as important in chronic and complex conditions as in care at the end of life. Such a framework may significantly decrease the morbidity and, indeed potentially, the mortality by better managing comorbid illness. Palliative care can have premature mortality just as in any clinical practice.

Implications for clinical practice

The population with chronic, complex or chronic progressive disease is at the above average risk for iatrogenic harm. Medications that have been appropriate and well tolerated earlier in a person's life may cause morbidity or even inadvertently hasten death without careful review. Prognostication requires appreciation of the natural history of life-limiting illnesses, the impact of concurrent comorbid illnesses, and the rate of change of function for individuals. Prescribing as prognosis worsens requires careful consideration as the benefit–harm balance shifts. Resetting goals of care explicitly with patients and their families requires explanation and negotiation.

Given the problems of multiple medications, which can be worsened with multiple prescribers[15], a single coordinating clinician must be identified. This is especially difficult at times of transition in place of care as this clinician may change. Careful consultation about the original intent of a medication is crucial.

Optimizing compliance with medications that are offering most benefit (or most harm if stopped abruptly) is essential if unnecessary or premature deterioration is to be avoided in a population with little reserve for any iatrogenic insult. Compliance may also, at times, be improved by considering alternative routes of administration for an existing medication.

Considered substitution of medications rather than cessation may reduce toxicity of individual medications or the cumulative effects of medications taken in combination (such as anticholinergic load). Judicious dose reduction and continued careful review will allow medications to be titrated accurately to minimize harm.

Implications for research

A theoretical framework for understanding how to adjust long-term medications already exists. Adding high quality empirical evidence to the process will take time. Early double-blind randomized controlled trials exploring the withdrawal of long-term therapy provide a crucial insight into a feasible and ethically acceptable

method of defining the evidence base needed for practice in this area[16].

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