When to stop?

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EDITORIAL

When to stop?

Duration and discontinuation of treatment are essential issues in drug prescribing. General practitioners (GPs) have to decide on the length of the therapy when writing a prescription and also have the responsibility to inform patients accordingly.

In Western countries, an increasing number of therapeutic drug groups are primarily prescribed by the GP [1–3]. Prescription data collected at a national level in Denmark in 2001–2005 [4] showed that more than 90% are dispensed by pharmacies servicing the primary health sector. A fraction of these treatments may have been initiated by hospital clinics or specialists, but the continued control of the treatments is largely the responsibility of the GP. Sometimes an ongoing treatment may prove not to be appropriate any more regardless of the time and place of initiation [5,6]. The decision to stop treatment most often has to be taken by the GP. If unnecessary treatments are continued it may lead to for example polypharmacy, side effects and unnecessary expense.

Optimal decisions on duration and discontinuation of drug therapies require that the GP has access to relevant and precise information on the subject. This information should in principle be evidence-based, i.e. founded on scientific data from randomized controlled trials. One might expect such information to be an integral part of national and international textbooks dealing with drug therapies as well as review articles and guidelines in the different fields of therapeutics. However, in many fields of drug therapy explicit recommendations concerning duration of therapy based on appropriate scientific documentation appear to be sparse or non-existent. Therefore we decided to examine the problem more systematically.

We evaluated the *recommendations* given in six internationally well-reputed textbooks dealing with drug therapy: three textbooks on clinical medicine [7–9], two textbooks on clinical pharmacology and therapeutics [10,11], and one book with review articles on evidence for existing therapies in healthcare [12].

Each book was assessed with regard to recommendations given for some of the drugs typically initiated in general practice (Table I). For

a classification of the recommendations given concerning duration and treatment, six categories were defined:

- A. No text on drug/indication.
- B. No mention of time limitations or optimal duration of therapy.
- C. Mention of possible time limitation, but no mention of optimal length of therapy, or only vague suggestions. Included mention of possible long-term adverse effects, drug dependence, loss of effect, etc.
- D. Specific recommendations for duration of therapy.
- E. Specific indication that the drug therapy is considered lifelong.
- F. Diagnostic discontinuation: Indication that therapy usually is lifelong, but that discontinuation may be recommendable to exclude false indication or recovery.

The evaluations were carried out by two of the authors. Divergences were resolved through discussion with the third author. We found good agreement on the ratings and all differences were small and easily resolved by re-examinations of the texts and discussion.

Table I shows the number of books for each scoring category (A–F). There was generally good agreement between the different books on the scoring for each drug/indication. Analyses of ratings for individual books revealed no consistent differences between books or types of books (clinical medicine vs. clinical pharmacology and therapeutics). Apart from being short of two of the evaluated drug/indications (score: A), BMJ Clinical Evidence [6] did not differ significantly from the other books.

Specific recommendation on duration (score D) was only a general feature for a few drug treatments/indications: anti-ulcer therapy largely linked to the *Helicobacter pylori* eradication scheme, antimycotics, antibiotics, anti-viral therapy, and antidepressants.

For drug-treatment/indications generally considered lifelong we only found one example in one textbook where this was explicitly indicated and in one other case diagnostic discontinuation was suggested.

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Table I. Drug therapy initiated in general practice: Textbook recommendations on duration and discontinuation of therapy.

ATC codes	Drug groups	Recommendations						Indications
		A	B	C	D	E	F	
A02BA+C	H2-receptor antagonists and proton pump inhibitors	<i>1</i>	<i>1</i>	<i>1</i>	<i>3</i>			Dyspepsia
A08	Anti-obesity drugs		<i>2</i>	<i>3</i>	<i>1</i>			Overweight
A10A	Insulin		<i>4</i>	<i>2</i>				DM, type 1&2
A10B	Oral antidiabetics		<i>4</i>	<i>2</i>				DM type 1&2
C01A	Digoxin		<i>5</i>	<i>1</i>				Cardiac failure, arrhythmia
C01D	Nitrates		<i>6</i>					Coronary syndrome
C03+07+08+09A+C	Antihypertensives ¹		<i>5</i>				<i>1</i>	Hypertension
C10AA	Statins		<i>5</i>			<i>1</i>		Hypercholesterol
C10AB	Fibrates		<i>6</i>					Hypercholesterol
D01A	Antimycotics (derm.)			<i>1</i>	<i>5</i>			Dermal fungal infection
D07	Glucocorticoids (derm.)		<i>3</i>	<i>3</i>				Dermatitis/eczema
G03A	Oral contraceptives	<i>1</i>	<i>4</i>	<i>1</i>				Contraception
G03C+D+F	Estrogen and/or progestogen		<i>4</i>		<i>2</i>			Bleeding disorder
H02A	Glucocorticoids (systemic)		<i>1</i>	<i>5</i>				Anti-inflammatory
J01	Antibiotics			<i>1</i>	<i>5</i>			Several infections
J05	Antivirals		<i>1</i>	<i>2</i>	<i>3</i>			Influenza, herpes simplex/zoster
M01A	NSAIDs		<i>6</i>					Anti-inflammatory
N02A	Opioids		<i>4</i>	<i>2</i>				Severe pain
N02C	Anti-migraine drugs		<i>6</i>					Migraine
N05B+C	Anxiolytics/hypnotics		<i>1</i>	<i>4</i>	<i>1</i>			Anxiety, sleep disturbances
N06	Antidepressants		<i>1</i>	<i>1</i>	<i>4</i>			Depression, acute
R03	Anti-asthma drugs		<i>1</i>	<i>5</i>				Asthma
R06	Antihistamines (systemic)		<i>6</i>					Allergic reactions

Notes: ¹Diuretics, betablockers, Ca antagonists, ACE inhibitors, Ang. tens. II inhibitors (five books only).

Recommendations – as given in the six reviewed books (see text): A: No text on drug/indication; B: No mention of time limitations or optimal duration of therapy; C: Mention of possible time limitations, but no mention of optimal length of therapy, or only vague suggestions; D: Specific recommendations for duration of therapy; E: Specific indication that the therapy is considered lifelong; F: Diagnostic discontinuation: Indication that therapy usually is lifelong, but that discontinuation may be recommendable to exclude false indication or recovery.

Numbers in *italics* indicate the number of books with the given recommendation score (A–F).

Explicit discussion of the treatment's duration was with a few exceptions only found for short-term regimens and nearly absent for therapies generally considered “chronic”. The textbooks investigated were selected on the basis of their general, international esteem and popularity, but the selection was indeed subjective. Other textbooks, international or national, could have a more practical approach to drug treatment per se and therefore give more specific advice. However, the homogeneity in our findings between the different books investigated was striking and supports the view that the results may be generalizable.

The presence or absence of specific recommendations may reflect the level of underlying clinical evidence as typically obtained from randomized controlled trials (RCTs). The frequent, specific recommendations for antimicrobial treatments may thus reflect the fact that duration of treatment is often an explicitly tested variable in RCTs in this field [13–16]. On the other hand, duration of treatment has not been addressed as a primary variable in RCTs on antisecretory medication if

Helicobacter pylori eradication schemes are disregarded and classified as antibiotic treatment [17–20]. For antidepressants four out of six textbooks gave specific recommendations on duration despite the fact that a literature search yielded only one original study with duration of treatment as a primary variable [21]. The recommendations given in the literature appear generally to be based on theoretical and clinical considerations [22–24].

As to the presumed “lifelong” treatments, such as lipid-lowering drugs, the general, often implicit recommendation in the literature is that once started the treatment should be lifelong, although little or no direct, hard evidence for the appropriateness of this strategy exists [25–28]. The inclusion of duration as a primary variable in RCTs on presumed lifelong treatments (lipid-lowering drugs, antihypertensives, antidiabetics, antiepileptics, etc.) may pose insurmountable clinical and ethical problems. The evidence must therefore often be sought from less strong data, such as observational studies, epidemiological research etc. However, discontinuation may prove to be possible [29].

It is our opinion that duration of drug therapy has received relatively little attention in the relevant literature, from RCTs to major textbooks. However, for the GP, with the primary responsibility for the vast majority of drug therapies, guidance concerning duration and discontinuation of drug treatment is indispensable. We hope more attention is paid to this issue in the future at all levels: the conduct of RCTs, meta-analyses, reviews, textbooks, guidelines, and regulatory.

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