Low drug doses may improve outcomes in chronic disease

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ABSTRACT

- The relationship between drug dose and clinical outcome has not been established for many medications used to treat chronic disease. Evidence is emerging that chronic diseases can be treated effectively with low doses.
- Adverse drug reactions account for significant morbidity and mortality and are generally dose related.
- Optimal drug dose — the best balance of benefit and risk — varies between individuals and may change over time. When treating chronic disease it is important to establish and maintain the optimal dose for each patient by close clinical monitoring.

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Chronic diseases are creating a growing burden of ill health as populations age[1] and become more obese,[2] and as survival from many conditions improves. Long-term pharmacotherapy is used increasingly to control symptoms and slow disease progression. Unfortunately, there is a dearth of reliable information about drug dosages for, and outcomes of, long-term treatment of physical and mental illness. Dosages recommended in clinical practice guidelines are usually derived from studies of acute and severe cases of disease. There is little research to support the application of these guidelines to long-term treatment regimens and to the large number of patients with mild cases of disease who are managed in primary care. In addition, few studies specifically address dosage.

Long-term pharmacotherapy carries the risk of adverse drug reactions that account for more than 5% of acute admissions[3] and around 7000 deaths per year in the United States.[4] High drug doses are associated with an increased risk of adverse effects, as shown with aspirin,[5] β-blockers,[6] angiotensin-converting enzyme (ACE) inhibitors,[7] statins,[8] opioids,[9,10] cyclo-oxygenase-2 inhibitors,[11] oral contraceptives,[12] cytotoxics,[13] antidepressants[14] and atypical antipsychotics.[15] Allergic reactions are also more likely with high doses.[16]

High drug doses are not necessarily more effective than low doses. For example, increasing the dose of a selective serotonin reuptake inhibitor for patients with major depressive disorder may not be associated with useful clinical improvements.[17] Moreover, low doses of opioids,[18] antidepressants,[14] antipsychotics[19] and lithium[20] are similarly effective to or marginally less effective than high doses, but are associated with appreciably fewer adverse effects. Of concern, adverse effects of psychotropics and symptoms of mental illness can overlap — for example, insomnia, fatigue, somnolence, nausea, sexual dysfunction and weight gain.[21,22] If these symptoms are incorrectly attributed to illness, they may be inadvertently perpetuated by increases in dose.

High doses used in acute severe disease are often decreased for maintenance purposes. Frusemide can be used at up to 160 mg daily for the treatment of acute pulmonary oedema, but decreased to 20–40 mg daily to prevent recurrence. Similarly, initial daily doses of 600 mg clopidogrel, 3 mg colchicine and 1200 mg amiodarone are typically decreased to maintenance doses of 75 mg, 0.5 mg and 200 mg, respectively.

However, many drugs are prescribed at or near maximum recommended doses for the treatment of chronic disease — including ACE inhibitors,[23] antidepressants[14] and antipsychotics[19] — despite the lack of good evidence that this is necessary. There are strategies for optimising therapeutic benefits other than increasing dose. For example, if a blood pressure target is not achieved with one drug, rather than increasing the dose and risk of adverse effects, drugs working through different mechanisms can be used with additive benefit but without additive adverse effects.[24] Similarly, the addition of low-dose dipyridamole to very low-dose aspirin reduces the risk of recurrent stroke and other vascular events by 23% compared with very low-dose aspirin alone.[25] Such additive effects form the basis of the polypill concept[26] and combination cytotoxic chemotherapy.

Lowest recommended drug doses are often not considered,[27] even in mild disease, probably because of concern about subtherapeutic dosing. However, the aim should be optimal dosing. Clinicians may prescribe high doses because clinical practice guidelines and specialist opinion often encourage aggressive treatment.[28] Higher-than-necessary maintenance doses may also be used because of insufficient communication between hospital specialists and general practitioners regarding dose adjustment during long-term follow-up.

The growing emphasis on aggressive treatment to target presents challenges for optimal dosing, as more intense treatment can be associated with significant adverse effects. For example, in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, more intense oral hypoglycaemic and insulin treatment increased weight, hypoglycaemia and mortality rate in patients with type 2 diabetes mellitus.[29] Another example is the atorvastatin Treating to New Targets (TNT) study, in which adverse events occurred in 8.1% of patients with coronary heart disease treated with 80 mg daily, compared with 5.8% in those treated with 10 mg daily.[30] This 40% increase in side effects included a sixfold increase in persistent elevation of alanine aminotransferase and/or aspartate aminotransferase levels. Statins can also cause myopathy,[8] type 2 diabetes[31] and cerebral haemorrhage.[32] Atorvastatin at 10 mg daily has been shown to reduce coronary events by more than 61% after 3 years,[33] and the TNT study appears to suggest that 80 mg daily can increase this benefit to 78%. However, instead of increasing the statin dose eightfold, cardiovascular risk may be further lowered more safely by lifestyle changes and appropriate antihypertensive and antiplatelet pharmacotherapy. Most of the published evidence demonstrating reduced cardiovascular events with statin therapy is in the low dose range,[34] even in patients with familial hypercholesterolaemia.[35]

With respect to outcomes, although haemodynamics improve more in patients with cardiac failure who receive 25 mg carvedilol twice daily than those who receive 6.25 mg twice daily, rehospitalisation rates are similar for both dosing regimens.[36] Also, reduced mortality of patients with cardiac failure who are treated with bisoprolol[37] or metoprolol,[38] compared with placebo, appears to be the same at different doses. Furthermore, there is evidence that

"less can be more" with respect to dose — lower doses of thiazide diuretics in hypertension are associated with fewer coronary events and deaths than are seen with higher doses,[39] and lower blood levels of digoxin in cardiac failure are associated with improved survival compared with higher levels.[40] Indeed, defined daily doses for 20 out of 27 cardiovascular drugs have decreased since they were first marketed.[41]

The use of low drug doses in chronic disease has become more prevalent, especially in primary care and particularly for remission maintenance. There is considerable evidence of good efficacy with much lower doses than in the past of a variety of established therapies — for example, aspirin for cardiovascular disease (75 mg[42] versus up to 650 mg daily), thiazides for hypertension (12.5 mg versus 50 mg daily),[39] spironolactone for cardiac failure (25 mg[43] versus 200 mg daily), inhaled fluticasone for asthma (175 mg versus 500 mg daily),[44] prednisolone for rheumatoid arthritis (5 mg[45] versus up to 25 mg daily) and haloperidol for schizophrenia (50 mg versus 200 mg monthly).[46]

High drug doses may be necessary to treat resistant disease, but dosage should be individualised during follow-up by close clinical monitoring and close communication between the specialist and primary care clinician. Due to wide variation between individuals — in body size and physiology, cytochrome P450 enzyme subtypes,[20] severity of disease, and comorbidities — wide ranges of optimal dose are to be expected. Pharmacogenetics may provide practically useful understanding of interindividual variation in drug metabolism and elimination in the future,[47] but clinical monitoring is paramount at present.

The case for low-dose pharmacotherapy in older patients is particularly pertinent. Adverse drug reactions are an important cause of hospital admissions in older people[48] for various reasons. Organ systems, particularly the central nervous system and cardiovascular system, are often diseased and potentially more sensitive to drug effects. Drugs accumulate with reduced renal[49] or hepatic function.

If low doses provide sufficient efficacy in chronic disease, the associated reduction in adverse effects should improve quality of life, particularly for drugs that affect the central nervous system, such as psychotropics and analgesics. The lowest effective dose is also likely to improve patient compliance with medication. Efficacy usually follows a sigmoid relationship with dose; however, as benefits plateau with increasing dose, adverse effects continue to increase. Therefore, the aim of optimal dosing is to achieve the best balance between benefit and risk. Furthermore, lifestyle changes involving diet, exercise, reduction in alcohol and tobacco consumption and appropriate management of psychosocial stress may reduce drug dose requirements in a range of chronic diseases. For example, although statins can decrease mortality by more than 20%[34] weight reduction with bariatric surgery can decrease mortality by 40%[50] by substantially reducing hyperlipidaemia, hypertension and type 2 diabetes.[51] Weight reduction with lifestyle changes should be equally effective and allow reduction of statin dose, and would also confer a broad range of other health benefits. However, we recognise that many patients find it difficult to achieve desirable changes in lifestyle.

In chronic disease, long-term care permits close individualised dose titration against key clinical and laboratory indicators to determine the dose at which improvement plateaus. This can be applied to dose reduction for drug therapy that begins in hospital. For treatment of mild illness in primary care, it is advisable to "start low and go slow" to avoid exceeding the optimal dose, particularly with drugs that have a narrow therapeutic window, such as digoxin. This may not be as important with drugs that have a wider therapeutic window, such as angiotensin receptor blockers. Close monitoring is essential to avoid undertreatment, especially as diseases often progress and dose increases may therefore be required.

The emerging evidence that low drug doses may be as effective as high doses in the management of chronic disease, with the advantages of reduced adverse effects and potentially improved quality of life, deserves systematic evaluation. In the absence of reliable research, differences in opinion among clinicians will remain. Sufficiently powered studies are needed to address important outcomes at different doses, and research is required to establish the best measures for reliable clinical monitoring that can guide optimal dosage. For new drugs in particular, wide ranges of dose should be evaluated with respect to long-term outcomes.

Competing interests

None identified.

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References

1 Tackling the burden of chronic diseases in the USA [editorial]. *Lancet* 2008; 373: 185.
2 Haslam DW, James WPT. Obesity. *Lancet* 2005; 366: 1197-1209.
3 Pirmohamed M, James S, Meakin S, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18,820 patients. *BMJ* 2004; 329: 15-19.
4 Chyka PA. How many deaths occur annually from adverse drug reactions in the United States? *Am J Med* 2000; 109: 122-130.
5 Fries JF, Rarney DR, Singh G, et al. A reevaluation of aspirin therapy in rheumatoid arthritis. *Arch Intern Med* 1993; 153: 2465-2471.
6 Salpeter RS, Orniston TM, Salpeter EE. Cardioselective β-blockers in patients with reactive airway disease: a meta-analysis. *Ann Intern Med* 2002; 137: 715-725.
7 Packer M, Poole-Wilson PA, Armstrong PW, et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. *Circulation* 1999; 100: 2312-2318.
8 Armitage J. The safety of statins in clinical practice. *Lancet* 2007; 370: 1781-1790.
9 Zhao SZ, Chung F, Hanna DB, et al. Dose–response relationship between opioid use and adverse effects after ambulatory surgery. *J Pain Symptom Manage* 2004; 28: 35-46.
10 Cherny N, Ripamonti C, Pereira J, et al. Strategies to manage the adverse effects of oral morphine: an evidence-based report. *J Clin Oncol* 2001; 19: 2542-2554.
11 Vardeny O, Solomon SD. Cyclooxygenase-2 inhibitors, nonsteroidal anti-inflammatory drugs, and cardiovascular risk. *Cardiol Clin* 2008; 26: 589-601.
12 Chasan-Taber L, Stampfer MJ. Epidemiology of oral contraceptives and cardiovascular disease. *Ann Intern Med* 1998; 128: 467-477.
13 Kaplan LD, Straus DJ, Testa MA, et al. Low-dose compared with standard-dose m-BACOD chemotherapy for non-Hodgkin's lymphoma associated with human immunodeficiency virus infection. *N Engl J Med* 1997; 336: 1641-1648.
14 Bollini P, Pampallona S, Tibaldi G, et al. Effectiveness of antidepressants. Meta-analysis of dose–effect relationships in randomised clinical trials. *Br J Psychiatry* 1999; 174: 297-303.

15 Ray WA, Chung CP, Murray KT, et al. Atypical antipsychotic drugs and the risk of sudden cardiac death. *N Engl J Med* 2009; 360: 225-235.
16 Vervloet D, Durham S. Adverse reactions to drugs. *BMJ* 1998; 316: 1511-1514.
17 Ruhe HG, Huyser J, Swinkels JA, Schene AH. Dose escalation for insufficient response to standard-dose selective serotonin reuptake inhibitors in major depressive disorder. *Br J Psychiatry* 2006; 189: 309-316.
18 Ballantyne JC, Mao J. Opioid therapy for chronic pain. *N Engl J Med* 2003; 349: 1943-1953.
19 Davis JM, Chen N. Dose response and dose equivalence of antipsychotics. *J Clin Psychopharmacol* 2004; 24: 192-208.
20 Mitchell PB. Therapeutic drug monitoring of psychotropic medications. *Br J Clin Pharmacol* 2000; 49: 303-312.
21 Papakostas GI. Tolerability of modern antidepressants. *J Clin Psychiatry* 2008; 69 Suppl E1: 8-13.
22 Lenze EJ, Rollman BL, Shear MK, et al. Escitalopram for older adults with generalised anxiety disorder. *JAMA* 2009; 301: 295-303.
23 Yusuf S, Sleight P, Pogue J, et al. Effects of an angiotensin-converting-enzyme inhibitor, Ramipril, on cardiovascular events in high risk patients. *N Engl J Med* 2000; 342: 145-153.
24 Law MR, Wald NJ, Morris JK, Jordan RE. Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. *BMJ* 2003; 326: 1427-1434.
25 Verro P, Gorelick PB, Nguyen D. Aspirin plus dipyridamole versus aspirin for prevention of vascular events after stroke or TIA. A meta-analysis. *Stroke* 2005; 36: 162-168.
26 Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. *BMJ* 2003; 326: 1419-1424.
27 Cohen JS. Avoiding adverse reactions. Effective lower-dose drug therapies for older patients. *Geriatrics* 2000; 55: 54-64.
28 National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand. Guidelines for the prevention, detection and management of chronic heart failure in Australia. Canberra: NHFA, 2006. http://www.heartfoundation.org.au/Professional_Information/Clinical_Practice/CHF/Pages/default.aspx (accessed Jul 2009).
29 Gerstein HC, Miller ME, Byington RP, et al. Effective of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008; 358: 2545-2559.
30 LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med* 2005; 352: 1425-1435.
31 Ridker PM, Danielson E, Fonseca FAH, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008; 359: 2195-2207.
32 Amarenco P, Bogousslavsky J, Callahan A, et al. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med* 2006; 355: 549-559.
33 Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *BMJ* 2003; 326: 1423-1429.
34 Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomized trials of statins. *Lancet* 2005; 366: 1267-1278.
35 Versmissen J, Oosterveer DM, Yazdanpanah M, et al. Efficacy of statins in familial hypercholesterolaemia: a long term cohort study. *BMJ* 2008; 337: a2423.
36 Bristow MR, Gilbert EM, Abraham WT, et al. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. *Circulation* 1996; 94: 2807-2816.
37 Simon T, Mary-Krause M, Funck-Brentano C, et al. Bisoprolol dose–response relationship in patients with congestive heart failure: a subgroup analysis in the cardiac insufficiency Bisoprolol study (CIBIS II). *Eur Heart J* 2003; 24: 552-559.
38 Wikstrand J, Hjalmarson A, Waagstein F, et al. Dose of metoprolol CR/XL and clinical outcomes in patients with heart failure (MERIT-HF). *J Am Coll Cardiol* 2002; 40: 491-498.
39 Psaty BM, Smith NL, Siscovick DS, et al. Health outcomes associated with antihypertensive therapies used as first-line agents. A systematic review and meta-analysis. *JAMA* 1997; 277: 739-745.
40 Rathore SS, Curtis JP, Wang Y, et al. Association of serum digoxin concentration and outcomes in patients with heart failure. *JAMA* 2003; 289: 871-878.
41 Heerdink ER, Urquhart J, Leufkens HG. Changes in prescribed drug doses after market introduction. *Pharmacoepidemiol Drug Saf* 2002; 11: 447-453.
42 Campbell CL, Smyth S, Montelescot G, Steinhubl SR. Aspirin dose for the prevention of cardiovascular disease. *JAMA* 2007; 297: 2018-2024.
43 Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999; 341: 709-717.
44 Holt S, Suder A, Weatherall M, et al. Dose–response relation of inhaled fluticasone propionate in adolescents and adults with asthma: meta-analysis. *BMJ* 2001; 323: 1-8.
45 Wassenberg S, Rau R, Steinfeld P, Zeidler H. Very low-dose prednisolone in early rheumatoid arthritis retards radiographic progression over two years. A multicenter, double-blind, placebo-controlled trial. *Arthritis Rheum* 2005; 52: 3371-3380.
46 Kane JM, Davis JM, Schooler N, et al. A multidose study of haloperidol decanoate in the maintenance treatment of schizophrenia. *Am J Psychiatry* 2002; 159: 554-560.
47 Evans WE, McLeod HL. Pharmacogenomics — drug disposition, drug targets, and side effects. *N Engl J Med* 2003; 348: 538-549.
48 Mannesse CK, Derkx FHM, de Ridder MAJ, et al. Contribution of adverse drug reactions to hospital admission of older patients. *Age Ageing* 2000; 29: 35-39.
49 Corsonello A, Pedone C, Corica F, et al. Concealed renal insufficiency and adverse drug reactions in elderly hospitalized patients. *Arch Intern Med* 2005; 165: 790-795.
50 Adams TD, Gress RE, Smith SC, et al. Long-term mortality after gastric bypass surgery. *N Engl J Med* 2007; 357: 753-761.
51 Buchwald H, Avidor Y, Braunwald E, et al. Bariatric surgery. A systematic review and meta-analysis. *JAMA* 2004; 292: 1724-1737.

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