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## Mental healthcare in low and middle income countries

Should not replicate the inefficient, inaccessible, and insensitive Western model

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The global burden of disease is shifting rapidly from infectious disease to chronic non-infectious disease, with mental and substance use disorders the leading cause of years lost to disability in 2010 worldwide.<sup>1</sup> Meanwhile, the movement for global mental health, largely based on evidence based treatments from wealthy countries, has been rapidly gaining momentum.<sup>2</sup> Evidence for the effectiveness of these treatments is, however, often silent on culture, context, and preferences of patients. The failure to listen to people and to consider context has led to substantial waste and harm in wealthy countries.<sup>3</sup> These concerns should be central in the global mental health movement and will be emphasised at the Salzburg Global Seminar session on mental health in December 2014, which will include teams from more than 12 countries.

Wealthy countries, whether they have market driven or state planned systems, have created expensive and inefficient mental healthcare. Government, industry, and experts make decisions at the top, while people who are at risk, those with serious illnesses, families, and particularly minority communities are left out of the decision making process and often out of the care system entirely. For example, even with the exorbitant healthcare spending in the United States, the mental health system fails to reach more than half of people with the most serious mental disorders.<sup>4</sup>

Low and middle income countries have limited resources to replicate healthcare systems in high income countries, but why should they emulate inefficient, inaccessible, insensitive systems? Alternative approaches may be more efficient, more scalable, and more sensitive to culture,

needs, and context.<sup>5</sup> Traditional models of mental illness in many countries emphasise recovery, non-medicalised approaches, families, religion, and extensive use of lay health workers. In addition, nearly all countries have widespread mobile phone networks that may permit progressive use of health technologies. Finally, not having to dismantle inefficient systems maintained by vested interests represents an enormous advantage.

### Listen to the people

Low and middle income countries could develop alternative behavioural health systems by emphasising a few strategies. They should start by listening to people and empowering citizens, families, traditional supports, lay health workers, cultures, and communities to define their needs and design systems they want. Well informed patients and families can express preferences and participate in creating systems of care, including technology tools, that respond to personal and community needs.<sup>6</sup> Mental health should be for everyone: all people benefit from maternal and

child health, strong families, education, stress management training, social support, meaningful work, and self management.<sup>7</sup> Local stakeholders understand context and prefer spending limited resources on these local services. Local learning communities could monitor outcomes, learn from data, engage in continuous quality improvement, and perhaps prevent medical fraud.

These countries should also continue to train lay health workers and generalists rather than specialists. Lay health workers, backed up by medical generalists (primary care nurses and doctors), currently provide over 90% of mental healthcare worldwide. They can learn to manage depression, anxiety, psychosis, and substance misuse, just as they learn to manage malaria, HIV, and tuberculosis. On the other hand, specialists tend to develop a selective inattention to matters outside their expertise, thereby missing context and creating silos of care, overdiagnosis, and overtreatment.<sup>8</sup> Wealthy countries are now spending billions of dollars trying to convert systems that are based

**Lay health workers, backed up by primary care nurses and doctors, currently provide over 90% of mental healthcare worldwide**

on specialists back into integrated models of care so that they can control excessive treatments.

Community based psychosocial interventions should be emphasised rather than drug treatments. Peer and family supports, meditation, employment, and technology tools are generally effective, have few side effects, and are more durable than psychiatric drugs.<sup>9-10</sup> Wealthy countries spend huge resources on medications, mainly because of advertising and lobbying rather than because they are effective; a rational mental health system would rely on judicious use of generic drugs. Engaging indigenous religious and healing communities is critical. For example, after 400 years of genocide, historical trauma, and attempts at forced assimilation, many Native American tribes in the US are developing and using culture bound treatments for medical problems.<sup>11</sup> Evidence based practices from wealthy countries often need to be adapted to local context and culture,<sup>12-13</sup> but disregard for traditional healing creates backlash by disrespecting cultural beliefs, workforces, and context.

Finally, low and middle income countries should embrace new technologies that can provide education, prevention, assessment, treatment of acute illnesses, and management of long term illnesses.<sup>10</sup> These tools extend the reach of healthcare workers and are often effective by themselves—generally as effective as well trained mental health professionals.<sup>10</sup> Most people with mental disorders accept and value these tools highly; the tools can be translated to other languages and cultures; and the mobile phone infrastructure to deliver them broadly exists already.

Building on their strengths, low and middle income countries have the opportunity to create innovative, efficient, and culturally sensitive mental health systems and avoid the mistakes of high income countries.

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Staying local

Researchers in the specialty are pessimistic and have recently demonstrated the insidiousness of the phenomenon, potentially fuelled by academic reward systems that incentivise bad practice

## Reporting of harms in systematic reviews and their primary studies

Badly done and biased

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In a linked paper, the Outcome Reporting Bias in Trials (ORBIT) collaborators report a new study on outcome reporting bias,<sup>1</sup> a sequel to their earlier groundbreaking publication.<sup>2</sup> Outcome reporting bias is defined as “selection (on the basis of the results) of a subset of the original variables recorded for inclusion in a study publication.” It can arise from selective non-reporting or incomplete reporting of an outcome, as studied by the ORBIT collaborators, or fully reporting a particular outcome selectively from among multiple outcomes. Selective non-reporting has the same impact on a systematic review as the failure to report a study altogether (“publication bias”), biasing the pooled estimate away from the null.

The earlier paper<sup>2</sup> considered benefit outcomes, whereas this new research investigated harm outcomes.<sup>1</sup> This is important research because harms are poorly reported.<sup>3</sup> Authors of systematic reviews are being encouraged to identify a primary harm outcome for each review as well as a primary hypothesised benefit,<sup>4</sup> and motivations for selectively reporting outcomes may vary for beneficial and harm outcomes. Kirkham and colleagues studied two cohorts of systematic reviews, one formed from new Cochrane reviews in 2012 and the other from reviews specifically evaluating harms.<sup>1</sup> The researchers investigated the reporting of primary harm outcomes both in the reviews and in studies included in the reviews. They devised a framework to classify studies according to their risk of outcome reporting bias and applied this to the primary studies in a sample of reviews.

Specific harm outcomes were reported in only 38% (92/243) of Cochrane reviews. Overall, 76% (705/931) of primary studies in the Cochrane reviews and 47% (4159/8837) of primary studies in the adverse event reviews did not report the relevant review's primary harm outcome, or did not report it in full. Many individual studies could not be identified because they had been excluded from reviews owing to having “no relevant data.”

In the sample of reviews and their studies assessed for outcome reporting bias, nearly one fifth of primary studies not included in reviews in fact reported the primary harm outcome in full, so authors of these reviews failed to identify the data. Outcome reporting bias was suspected in over 63% (248/393) of the remaining primary studies.

Two crucial pieces of information are missing from Kirkham and colleagues' paper—namely, the sensitivity and specificity of “suspecting” a study to be at risk of outcome reporting bias and the impact of suspected bias on the findings of reviews. The authors did not interview individual trialists, as they had done in their earlier study.<sup>2</sup> The good news is that, in collaboration with *The BMJ*, they plan in the future to interview trialists

during the peer review process to understand better the “mechanisms for outcome reporting bias across both benefit and harm outcomes.”

There are familiar lessons from the study for review authors, trialists, and patients. Review authors should include harm outcomes in their review where relevant,<sup>4</sup> not exclude primary studies just because they do not report “any relevant data” for the outcome of interest,<sup>4</sup> and include non-randomised studies, if necessary—for example, because a

harm outcome is rare or occurs a long time after treatment, making it unlikely to be observed in randomised controlled trials.<sup>3 5 6</sup>

When designing, conducting, and reporting studies, trialists need to consider the perspective of the systematic review to which the trial will eventually contribute. They must write detailed protocols and analysis plans and follow them to minimise the scope for outcome reporting bias when reporting findings<sup>7 8</sup>; describe deviations from planned outcomes transparently; describe clearly outcomes that were measured, analysed, and compared; describe how harms were collected<sup>3</sup>; and make all data about harms available (numerators and denominators, to the level of resolution coded in the trial).<sup>3</sup> There is no excuse in the era of e-publishing and the internet for failing to make data on harms available. There are similar lessons for pharmacoepidemiologists doing non-randomised studies. They should register such

studies investigating harms and write and follow detailed analysis plans, being careful to distinguish between primary, secondary, and exploratory harm outcomes when planning their studies.

Patients are increasingly consulting systematic reviews. They should post comments on reviews that do not report harms or a primary harm outcome. Those who volunteer for trials should check with the research team that all harm data will be placed in the public domain. If patients help to hold researchers to account, the situation may improve.

### Against cherrypicking

What about the other side of the selective reporting coin; the tendency for researchers to selectively report the most positive finding from among all the available findings? Another recent review highlights the varied ways in which selective reporting of this kind can happen.<sup>9</sup> This problem is less well researched, at least as serious, and extremely difficult to investigate because protocols and prespecified analysis plans often do not include sufficient details, and analysis plans are rarely in the public domain. Without these documents as a template for analyses and reporting, there are plenty of opportunities for trialists to select one result from among many—and nothing for methodologists to check against. A new tool for non-randomised studies provides a framework for review authors to assess the risk of this kind of bias.<sup>10</sup>

The candour of the quotation at the start of Kirkham and colleagues' paper is striking and the table from which it is drawn is sobering (table 3 from Smyth et al, doi:10.1136/bmj.c7153). These disturbing quotes suggest that many trialists are naive and often paternalistic—completely failing to think beyond their own study to the wider evidence base. Are things improving? Kirkham and colleagues' study does not address the question, but I suspect not. Researchers in the specialty are pessimistic<sup>11</sup> and have recently demonstrated the insidiousness of the phenomenon, potentially fuelled by academic reward systems that incentivise bad practice.<sup>12</sup> We may be glimpsing just the tip of the iceberg.

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No change

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**It is clearly time for NICE to re-evaluate its guidance on one step nucleic acid amplification**

## Intraoperative assessment of axillary lymph nodes in breast cancer

### Time to abandon?

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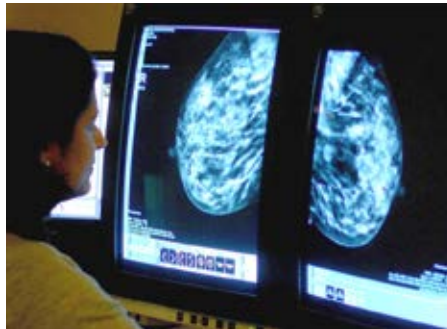
The main advantage of intraoperative assessment of axillary lymph nodes in patients having surgery for breast cancer is that metastatic disease can be diagnosed and removed in a single operation. However, there are several disadvantages that have cast doubt on its use. These include concerns about its accuracy and the uncertainty that all patients with diseased sentinel nodes need additional treatment.

Several methods have been used for intraoperative assessment of axillary nodes, including frozen section analysis, touch preparation cytology, and one step nucleic acid amplification. The National Institute for Health and Care Excellence (NICE) approved one step nucleic acid amplification in 2011, and it is the most widely used axillary staging method in the United Kingdom.<sup>1</sup>

A recent meta-analysis has raised doubts about the ability of this method to accurately determine the extent of axillary node involvement.<sup>2</sup> The method is based on the measurement of messenger RNA for cytokeratin 19, expression levels of which vary between and within cancers, with copy numbers ranging from 4700 to 140 000 copies per microlitre. The meta-analysis concluded that the wide range of copy numbers in a fixed tumour volume precluded the accurate identification of macrometastases ( $\geq 2$  mm) in lymph nodes.<sup>2</sup> The positive predictive value of this method compared with histology was only 0.79, and the authors concluded that up to 21% of patients found to have positive lymph nodes using this method had micrometastases and therefore did not require axillary clearance. It is clearly time for NICE to re-evaluate its guidance on one step nucleic acid amplification.

### Is treatment really necessary?

Doubts that patients with positive nodes require additional treatment stem from a pivotal US trial.<sup>3</sup> It found no survival benefit for patients with clinically node negative breast cancer who received axillary radiotherapy or axillary clearance com-



**Look but don't touch**

pared with those whose nodes were treated only when they became palpable. More recently, the American College of Surgeons Oncology Group Z0011 trial evaluated axillary node dissection in clinically node negative patients having breast conserving surgery, whole breast radiotherapy, and adjuvant systemic treatment.<sup>4</sup>

It compared the outcomes in patients with one or two positive sentinel nodes randomised to axillary lymph node dissection or sentinel lymph node biopsy alone. At median follow-up of 6.3 years there was no difference in the axillary recurrence rates between groups (0.5% versus 0.9%, respectively) and no improvement in survival with axillary lymph node dissection. Although this trial recruited fewer patients than originally planned, the findings were statistically valid.<sup>4,5</sup> The death rate was low in both arms of the trial, almost certainly because patients received effective systemic therapy, thus reducing the chances that axillary surgery could have influenced survival. Axillary lymph node dissection did, however, significantly increase the rate of lymphoedema.<sup>5</sup>

Two trials have since confirmed that patients with small volume axillary nodal disease do not require axillary lymph node dissection. The NSABP B-32 trial randomised 5600 patients with clinically node negative breast cancer to receive either axillary lymph node dissection or sentinel lymph node biopsy alone.<sup>6</sup> Over 4000 of the patients were pathologically node negative on haematoxylin and eosin staining, and immunohistochemistry identified axillary nodal micrometastases or isolated tumour cells in 616 of these patients. At 10 years there was no significant benefit in local control or overall survival in patients with micrometastases who had axillary

clearance compared with those who had sentinel node biopsy alone. Similarly, a large randomised European trial found no benefits in disease control or survival for axillary node dissection compared with sentinel node biopsy alone in patients with micrometastases ( $< 2$  mm).<sup>7</sup> These and other studies led the American Society of Clinical Oncology to advise that patients with one to two positive nodes on biopsy who have breast conserving surgery, whole breast radiotherapy, and similar clinical and pathological characteristics to those enrolled in the Z0011 trial do not require routine axillary lymph node clearance.<sup>8</sup>

Axillary radiotherapy is an alternative to complete axillary lymph node dissection for patients with sentinel lymph node metastases. Studies performed 30 years ago compared axillary radiotherapy with axillary lymph node dissection and showed no difference in survival.<sup>9,10</sup> More recently, a large study compared axillary radiotherapy with axillary lymph node dissection in patients with a positive sentinel node and showed no significant difference in the rates of axillary recurrence and survival.<sup>11</sup> However, the lymphoedema rate with axillary radiotherapy was half that seen in patients treated with lymph node dissection. Therefore, for women who are likely to benefit from axillary treatment, radiotherapy is a viable alternative to axillary dissection, offering similar rates of disease control but lower rates of morbidity.

Given the results from randomised trials, the guidelines from the American Society of Clinical Oncology, and the alternative options available for patients with diseased nodes, it seems unnecessary for patients to have intraoperative axillary lymph node assessment. Decisions about how to treat axillary nodal disease should be made with knowledge of tumour biology, the burden of disease in the sentinel nodes, and any planned radiotherapy and systemic therapy. Most importantly, patients need to participate in these decisions. Intraoperative frozen section analysis of breast tumours was abandoned long ago because it denied patients the opportunity to contribute to their treatment planning. It is now time to do the same with intraoperative sentinel lymph node assessment.

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**A recent survey found that over 90% of patients would be willing to stop taking one or more of their medicines**

## Discontinuing drug treatments

We need better evidence to guide deprescribing

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Deprescribing is the process of withdrawing drugs in an attempt to improve patient outcomes. Emerging evidence from studies of patients with multimorbidity and older people, who are a large and growing proportion of the population, shows that deprescribing may be linked to improvements in survival and quality of life.<sup>1-2</sup> While it is sometimes asserted that patients are unwilling to have their drugs withdrawn, in a recent survey over 90% of patients reported that they would be willing to stop taking one or more of their medicines.<sup>3</sup> Deprescribing should be considered during every regular review of a patient.

The principles of prescribing and deprescribing are highly comparable,<sup>4</sup> although with obvious differences. Prescribing new drugs involves diagnosing a problem and establishing an indication; deprescribing involves establishing which drug may be causing a problem (an adverse drug event) or which drug does not have a current indication. Prescribing involves applying specific disease based guidelines to a patient; deprescribing involves optimising all treatments to achieve individual care goals. While prescribing for people with multimorbidity is commonly driven by guidelines that are based on single diseases, the deprescribing process aims to make the best and safest use of drug treatments in adults with multiple conditions who may be taking many different drugs (polypharmacy). This approach is particularly important among older people in whom multimorbidity and polypharmacy are common.<sup>5-6</sup>

The potential harms associated with deprescribing may include withdrawal reactions, rebound phenomena, and the reappearance of symptoms. Indeed, the ethical considerations of deprescribing are the same as those of any other medical intervention.<sup>7</sup> Deprescribing is not informed by current single disease guidelines or clinical trials,

and a specific evidence base is needed urgently to help provide guidance on drug withdrawal. This evidence could be gathered at several stages of the drug development and post-marketing processes, and the drug industry and researchers must collect and publish such data consistently.

### Developing an evidence base for deprescribing

To date, deprescribing or interventions to reduce the drug burden have mostly been targeted at specific patient subgroups, such as older people. Current data on the outcomes of deprescribing are inconsistent: study results vary depending on the setting and on the intervention being evaluated.<sup>8-9</sup> The evidence shows that multidisciplinary interventions can help reduce the drug burden; their effects on clinical outcomes are less clear, although emerging evidence has shown that deprescribing strategies targeting specific populations and drug classes may improve outcomes. For example, a non-randomised trial of polypharmacy reduction in older people showed that over half of drugs could be discontinued and that this reduction in the drug burden was associated with improvements in cognition and global health.<sup>1</sup>

Studies of deprescribing are in progress internationally. In Europe a multinational randomised controlled trial (RCT) that uses electronic decision support to guide deprescribing recently started in older people who are taking multiple drugs for chronic diseases ([www.prima-eds.eu/](http://www.prima-eds.eu/)). Further trials testing the clinical effects of interventions to reduce polypharmacy are under way in Australia (the Opti-Med study, a blinded RCT based on the Good Palliative-Geriatric Practice algorithm<sup>1</sup>; ACTRN12611000370909), Canada (Effect of Medication Minimization on Mortality and Hospitalization in Long Term Care Residents (WiseMed)—an open RCT; NCT01932632), and the Netherlands (Discontinuing Inappropriate Medication in Nursing Home Residents (DIM-NHR)—a cluster RCT; NCT01876095).

Other ongoing studies have focused on withdrawing specific drug classes, such as the sedative and antipsychotic drugs often prescribed to older people in residential care. In Australia the Halting Antipsychotic Use in Long Term Care (HALT) study is testing a model for deprescribing antipsychotics that provides nursing expertise to help manage challenging behaviours

(ACTRN12614000309684), and the Reducing Use of Sedatives and Aged Care Facilities (RedUse) study is testing interventions delivered by a pharmacist (ACTRN12608000221358). Canadian researchers, meanwhile, are developing evidence based guidelines on deprescribing specific drug classes.<sup>10</sup>

Plenty of opportunities exist for measuring outcomes associated with deprescribing within the current drug development process as part of phase I-IV studies of dosing, safety, and efficacy, and phase V studies of comparative effectiveness. In each of these phases participants stop drug treatments either owing to adverse effects, or because of withdrawal for other reasons, or simply because they have reached the end of the trial. Deprescribing trials could be embedded in the current phases of drug development (eg, phase III-a) or could be given a new trial phase ("VI") of drug development specifically to implement deprescribing trials.

A complementary approach may be to use large electronic medical databases to assess outcomes in patients whose drugs are discontinued as part of routine care.<sup>11</sup> In the United States the Patient Centered Outcomes Research Institute has launched an initiative to build a nationwide healthcare infrastructure to support the conduct of trials. Similarly, the European Medicines Agency has proposed a number of strategies in Europe to encourage better use of electronic databases and infrastructure during the drug development cycle, pre- and post-market.

Given that increasing numbers of deprescribing trials are being conducted, guidance is clearly needed on their design, conduct, and reporting. We recommend that policy makers, industry, and researchers debate the addition of a new drug development phase for such trials and consider adding specific guidance to the current CONSORT reporting statement.<sup>12</sup> A CONSORT extension for deprescribing trials could improve reporting generally, but it could also emphasise clear and detailed reporting of the intervention under study. Both of these are essential if we are to develop robust trial evidence to inform clinical decisions and policies on deprescribing.

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