**SLUG: COMMENT**

**TITLE: The crisis in Cochrane: Evidence Debased Medicine**

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The first articles by Iain Chalmers announcing the Cochrane Collaboration appeared in 1992 (1). Writing *The Antidepressant Era* in 1995, I characterised systematic reviews as a logical, and necessary medical development (2). From the mid-1990s, the United Kingdom (UK) became Cochrane central with many groups undertaking reviews.

The idea of embodying Evidence Based Medicine (EBM) in Guidelines also took shape at this time. In Britain, in 1997 a Labour government created a National Institute for Clinical Excellence (NICE) which began issuing Guidelines underpinned by Cochrane methods and in some instances with Cochrane collaboration. The NICE process was and still is highly regarded, sufficiently so for the Labour government to issue a new plan for Britain’s National Health Service (NHS) that on the basis of newly minted standards of care set about standardising the health service in a manner that embraces continuity of data, with an interchangeability of personnel, rather than continuity of care.

In 2004, a world no-one suspected came into view. As part of an FDA review of pediatric antidepressant trials at this point, it became clear that all trials in pediatric depression were negative, that all published studies were ghost or company written, in all cases the data were inaccessible and in the case of the published studies the publications were at odds with the data regulators revealed. The data on both benefits and harms was systematically distorted in publications even in the leading medical journals. This came to a head over the issue of suicide in 2004, when New York State filed a fraud action against GlaxoSmithKline (GSK), primarily on the basis that a ghost-written publication of Study 329 claimed paroxetine worked for and was safe for children who were depressed, when in an internal review it had recognised it didn’t work and had opted to pick out the good bits of this study and publish them (3).

This led reviewers within NICE, then compiling Guidelines for the treatment of pediatric depression, to publish an editorial “Depressing research” which raised a question as to whether it was possible in the circumstances revealed by these trials to undertake systematic reviews or write guidelines (4).

The issue of lack of access to the data and ghost writing of publications was therefore “known” within the Cochrane collaboration and Guideline apparatus as of 2004. This is not a feature of paediatric antidepressant trials alone, as what had been revealed appeared to be standard industry operating mode.

Cochrane, NICE, and other guideline bodies, however, suppressed this awareness. Peter Gøtzsche, and later Tom Jefferson, have been the exceptions to this rule. Beginning in 2009, Gøtzsche began to lobby the European ombudsman for access to clinical trial data, and put the issue of access to data on the map. Jefferson, with others, chased missing studies on Tamiflu and as studies came to light he and colleagues progressively revealed a picture of vanishing efficacy for this drug.

This process has led both Gøtzsche and Jefferson to encourage Cochrane reviewers to work from internal company Clinical Study Reports (CSRs), in addition to publications, and, latterly, as the issue of treatment related harms has become more salient, to question whether reviews are possible without the data. Their efforts have received support from many, but not all their colleagues.

Faced with stonewalling by regulators, the guideline apparatus, mainstream medicine, journals, and with very little support, it has taken distinct personal qualities on the part of both Gøtzsche and Jefferson to pursue this course. Both men have called things as they are when others have been unwilling to do so.

In the case of Gøtzsche, these personal qualities appear to have provided a basis for Cochrane to expel him in October 2018. As a director of a Cochrane centre and a Cochrane council member, Gøtzsche came into regular contact with the management of what had once been called a Cochrane Collaboration but had become Cochrane™, complete with a management apparatus. Gøtzsche’s forthright approach alienated some of the organisation’s management.

Allied to this, several weeks before the board meeting that led to his expulsion, Gøtzsche and Jefferson had publicly branded a Cochrane review of HPV vaccines as untrustworthy and as a betrayal of Cochrane’s core mission (5).

The Cochrane board members split over Gøtzsche’s expulsion. Almost half the board resigned. A large number of Cochrane centres around the world wrote expressing their support for Gøtzsche.

Cochrane centres are not funded by Cochrane™. They generate their own funds from national or provincial governments or other sources. The directors of these centres have, therefore, a certain independence. The calculations as to what to do, however, are not simple in all cases. Centre directors have “mouths to feed”. While supporting Gøtzsche might not initially lead to difficulties, some directors appear to believe that it opens them up to being pushed aside if another group sets up in their area and attracts the funding on the basis of an affiliation with the central organisation.

Cochrane and its directors face a crisis. Every decision has consequences.

In 2016, Jeremy Hunt, Britain’s then Minister of Health stated that children’s mental health was the greatest point of failure of the NHS (6). As of 2016, senior personnel in NICE had a *de facto* policy of not sharing a platform with anyone who might state that their Guidelines were based on ghost written articles and were prepared without access to the data that outside observers in general assume underpin them.

In 2018, children and their apparently deteriorating mental health was a regular and prominent feature in North American and European news features. BBC ran two primetime flagship programmes on the issue of children’s mental health and the use of antidepressant medicines. Both programmes were briefed on the contents of an article then in press (7), which outlined that as of 2018, it appears that every single one of the 30 RCTs of antidepressants undertaken in childhood depression, involving over 10,000 children, have been negative on their primary outcome measures, and all appear to show an excess of suicidal events on active treatment compared to placebo. Both programmes were made aware of data from the Centers for Disease Control (CDC) that despite the results of these studies, antidepressants now appear to be the most commonly used drugs by teenage girls except for oral contraceptives.

Both programmes were told that Prozac (fluoxetine) had been licensed for use in paediatric depression by American and European regulators in 2001 on the back of two negative trials. The licensing took place before concerns about pediatric antidepressants became widely known in 2004. From 2004 onwards, regulators and guideline bodies have continued to state that the pediatric fluoxetine trials are positive, when in fact on their primary outcome measures they are negative and as with other treatments there is an excess of suicidal acts on fluoxetine compared to placebo – in one trial 34 suicidal acts on fluoxetine compared to three on placebo but these data are effectively hidden (8).

Both programmes balked at airing these issues. One of the two made it clear that they had made enquiries of NICE in respect of the Prozac data and that NICE had refused to comment.

As outlined above, there is nothing unusual about paediatric depression. The evidence in this domain is produced in the same way as in any other medical domain.

As of 2018, the *BMJ* and other journals have carried several articles on falling or stalling life expectancies in several developed countries (9). There is no generally accepted explanation for this. A possible contributing factor lies in the fact that more than 50% of people over the age of 45 in the USA are now on 3 or more medicines and more than 45% of over 65s are on 5 or more medicines (10, 11). These data, allied to evidence that reducing medication burden to 5 medicines or less per day has the potential to reduce hospitalisation rates and extend life span, in addition to improving quality of life (12), suggest that poly-prescribing is having a detrimental effect on our overall health.

The current figures for medication consumption are almost certainly driven by a hyping of the benefits of medicines and hiding of their harms in ghost-written articles accompanied by a lack of access to the data from studies undertaken. If this has a similar effect on health more generally as it appears to be having on children’s mental health, then the current crisis in Cochrane represents a watershed moment in modern medical history.

While every director of a Cochrane centre has a responsibility to the mouths they have to feed, the Cochrane organisation should not tolerated a further 15 years’ worth of reviews based on ghost-written articles with a lack of access to trial data. This has been as deep a betrayal of the core Cochrane mission as it is possible to imagine.

References

1. Chalmers I Chalmers I, Dickerson K, Chalmers TC (1992). Getting to grips with Archie Cochrane’s Agenda. British Medical Journal 305, 786-788.
2. Healy D The Antidepressant Era. Harvard University Press, Cambridge Ma,1997
3. Study329.org
4. Lancet Editorial, Depressing Research. Lancet 363, (2004), 1335.
5. Jørgensen L, Gøtzsche PC, Jefferson T. The Cochrane HPV vaccine review was incomplete and ignored important evidence of bias. 0.1136/bmjebm-2018-111012
6. Campbell D. Jeremy Hunt says children’s mental health services are the NHS’ biggest failing. The Guardian October 20, 2016. https://www.theguardian.com/society/2016/oct/20/jeremy-hunt-promises-better-mental-health-services-children-adolescents
7. Healy D, Le Noury J, Jureidini J. Pediatric antidepressants: risks and benefits. International Journal of Risk and Safety in Medicine 2018, 30, 1-7.
8. Hogberg G, Antonuccio D, Healy D (2015). Suicidal Risk from TADS Study Was Higher than it First Appeared. Int J Risk & Safety in Medicine 27, 85-91. DOI 10.3233/JRS-150645
9. Hiam L, Harrison D, McKee M*, et al* Why is life expectancy in England and Wales ‘stalling’? *J Epidemiol Community Health* 2018. doi: 10.1136/jech-2017-210401
10. Ho JY, Hendi AS. Recent trends in life expectancy across high income countries. BMJ 2018, 362, k2562.
11. Pratt LA, Brody DJ, Gu Q (2017). Antidepressant Use Among Persons Aged 12 and Over: United States, 2011–2014. NCHS Data Brief No. 283, August 2017
12. Garfinkel, D; Mangin, D (2010). Feasibility study of a systematic approach for discontinuation of multiple medications in older adults. *Arch Intern Med*. **170** (18): 1648–54. [doi](https://en.wikipedia.org/wiki/Digital_object_identifier):[10.1001/archinternmed.2010.355](https://doi.org/10.1001%2Farchinternmed.2010.355).