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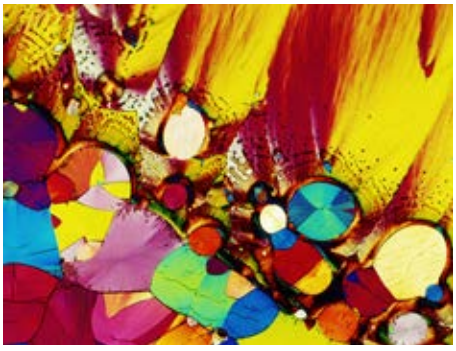
SEROTONIN AND DEPRESSION

Healy does a disservice to psychiatrists



Crystal myth

Healy does a great disservice to jobbing psychiatrists with his editorial on serotonin and depression, the marketing of a myth.[1] By portraying them as "co-opted into a myth" about low levels of serotonin being the sole cause of depression he paints them as gullible. And by stating that this theory is "an easy shorthand for communication with patients" he paints us as lazy and reductionist in our appraisal of the complex and diverse causes of depression.

Good psychiatrists have always been ready to admit that they are unsure how antidepressants work. Serotonin does have an important role—probably through factors such as neurogenesis and gene expression downstream from synapses[2 3]—but modern psychiatry is way ahead of where Healy seems to think it is. The picture is far more complex. The fact that ketamine has been shown to be useful in depression does not "cast doubt on the link between serotonin and depression;" rather, it confirms that the neurobiological underpinnings are as multifaceted as we think.[4]

In any case, whatever their mode of action, selective serotonin reuptake inhibitors (SSRIs) work. Even the most stringent of analyses (Kirsch et al) support this.[5] There is no good evidence that SSRIs work any less well than tricyclic antidepressants for depression. SSRIs have not become so common in clinical practice because of a pharma-doctor conspiracy, as Healy suggests, but because the older TCAs have a worse side effect profile and are lethal in overdose.[6] The safety of our patients should always come first, and they are far less safe without treatment for their depression.

Alexander E Langford core trainee in psychiatry, South London and the Maudsley NHS Foundation Trust, Bethlem Royal Hospital, Beckenham BR3 3BX, UK
alexander.langford@slam.nhs.uk

1 Healy D. Serotonin and depression. *BMJ* 2015;350:h1771. (21 April.)

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A "fact of the matter" may not exist in scientific narratives

Healy's observations on serotonin and depression make interesting, if familiar, reading.[1 2] However, I was struck by the remarkable claim that the focus on serotonin has led to the "eclipse of cortisol" in mood disorder research. A quick search in Scopus with "cortisol" and "depression" identified a rapidly increasing number of articles published since the late 1990s until the present time. Only last year a large placebo controlled study on the effects of inhibiting cortisol synthesis in patients with depression refractory to selective serotonin reuptake inhibitors (SSRIs) was completed in the UK.[3]

Healy also suggests that ketamine has been shown superior to SSRIs in melancholic depression, even though no such comparison has been carried out. He also implies that Andrews and colleagues' work is based on the intellectually paralysing notion that low serotonin causes depression, whereas in fact these authors argue exactly the opposite.[4]

Should we confront myths by constructing different ones? As an avid reader of *The BMJ* I find myself increasingly confused by this question. For if scientific narratives are manifestations of competing power claims and vested interests perhaps there isn't really a "fact of the matter"—the important thing is to be on the right side. I agree with Healy.

Philip J Cowen professor of psychopharmacology, University of Oxford, Warneford Hospital, Oxford OX3 7JX, UK phil.cowen@psych.ox.ac.uk

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Personalised pharmacotherapy: an interim solution?

Healy's engaging historical perspective on the rise of selective serotonin reuptake inhibitor (SSRI) antidepressants questions the efficacy and biological plausibility of these drugs.[1] However, his focus on low serotonin levels is irrelevant to whether SSRIs are effective treatments for depression. Importantly, the response to SSRIs seems to be heterogeneous rather than universally poor.

Unbiased trajectory based analysis of more than 2500 patients treated with SSRIs or placebo indicated that most patients (>75%) given an SSRI showed a superior response to those given placebo. However, nearly a quarter of patients treated with SSRIs showed a poorer response than those treated with placebo. This suggests that, in these patients, SSRI treatment interferes with their capacity to mount a placebo response, or perhaps even their capacity for resilience to depression.[2] This raises the important question of whether patients who seem to be better off avoiding SSRIs could be identified and diverted to other treatments for depression.

Our inability to personalise pharmacotherapy—to predict which patients will respond to specific antidepressants—is one factor that reduces the effectiveness of antidepressants. Currently, the process of matching patients and treatments requires a prolonged period of trial and error, delaying clinical improvement and increasing the risks and costs associated with treatment. Despite important progress in trying to identify depressed patients at high risk of treatment resistance,[3] psychiatry continues to lag behind other specialties like cardiology and oncology, in which personalised treatment is far better established.[4 5]

The development of more generally effective and more rapidly effective treatments would be important advances for public health. However, as an interim solution, we advocate the development and implementation of innovative statistical methods to get the best available drug to each patient. Personalised pharmacotherapy may still enable us to "save lives and restore function." Giving up on these patients is not an option.

Adam M Chekroud candidate for doctor of philosophy degree, Department of Psychology, Yale University, New Haven, CT 06511, USA
adam.chekroud@yale.edu
John H Krystal professor, Department of Psychiatry, Yale University

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Author's reply

I wrote an almost identical editorial in 1991.[1 2] Covering the marketing of serotonin in 1997,[3] I cited Jerome Gaub's 1767 opinion of Leibniz's

views on the relations between mind and body—it is a "fable whose novelty has recommended it, whose recommendation has spread it, whose spread has polished it, refined and adorned it with . . . a pleasing look of truth."[4]

I use selective serotonin reuptake inhibitors (SSRIs). Nevertheless I believe the SSRI era will soon stand as one of the most shameful in the history of medicine. The shame does not stem from what drug companies have done, which is only what might have been expected, but from the failure of doctors to know as much as they should have done about drugs they dish out so liberally. A recent study showing how a dollop of neuroscience dressing can disguise otherwise meaningless material should be compulsory reading for doctors who are, after all, the true consumers of these drugs.[5-8]

But perhaps an even greater shame will be seen to lie with the fact that, during this era, most publications on on-patent drugs in our best journals were ghost-written. In addition, during this time journals refused to demand access to trial data as the price for publication—this is most clearly demonstrated in the area of antidepressant studies on children. It has been an era when industry has controlled journals, by spending money on some of them and by intimidating others.

David Healy professor of psychiatry, University of Bangor, Bangor, UK
David.Healy54@googlemail.com.

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DEPRESSION IN CHILDREN

Challenges to primary care in managing depression in children

The National Institute for Health and Care Excellence (NICE) guideline summary recommended that Child and Adolescent Mental Health Services should work with primary healthcare professionals to develop systems for detecting, assessing, supporting, and referring depressed children and young people, with provision for those who are less seriously affected within primary care.[1] This recommendation does not take into account the challenges to primary care services in fulfilling this role.

A survey of UK GPs found that many GPs feel ill equipped to deal with young people's emotional distress and lack clarity about managing psychological difficulties.[2] Education and training in discriminating between emotional distress and clinical depression in young people, coupled with management techniques appropriate for primary care, are needed to facilitate compliance with NICE guidance.

We have reported on the development and evaluation of a programme (TIDY: therapeutic identification of depression in young people) that trains primary care practitioners (PCPs), GPs, and primary care nurses to differentiate between emotional turmoil and depression, and to implement setting appropriate management techniques. Our research has shown that it is feasible to train PCPs in the implementation of this programme, and that the programme is acceptable to PCPs and young people and can potentially reduce associated functional impairment.[3] Nevertheless, this work has also identified concerns among PCPs about managing emotional distress in young people,[4] including the unnecessary medicalisation of distress and the burden of broadening the PCP role.

Although evidence exists from the US,[5] demonstration of efficacy in the UK is required before PCPs engage in this work more fully. Investment in relevant research is needed before NICE guidelines can be implemented and the opportunity for intervention for young people can be realised.

Tami Kramer consultant child and adolescent psychiatrist, Westminster Child and Adolescent Mental Health Services, London NW8 0PJ, UK
t.kramer@imperial.ac.uk
Lorraine Als research psychologist
M Elena Garralda emeritus professor, Imperial College London, Centre for Mental Health, Hammersmith Hospital Campus, Imperial College London, London, UK

1 Hopkins K, Crosland P, Elliott N, et al; on behalf of the Clinical Guidelines Update Committee B. Diagnosis and management of depression in children and young people. *BMJ* 2015;350:h824. (4 March.)

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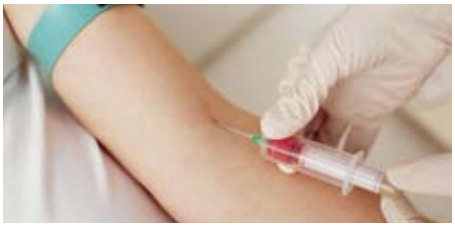
NON-INVASIVE PRENATAL TESTING

Non-invasive prenatal testing should be monitored properly



IAN HOOTON/SPL

Chitty and Kroese's editorial on realising the promise of non-invasive prenatal testing (NIPT) based on cell-free DNA in maternal plasma reaffirms the concept of superior performance compared with conventional screening.[1] However, the comparison was performed with standard first trimester screening and not with other screening methods that have higher sensitivity and specificity.[2] The same team carried out a study in a cohort of 452 901 women, 74% of whom were under 35 years of age.[3] Abnormal karyotypes were less likely to be identified with cell-free DNA than with sequential screening (75.4% *v* 81.6%). Overall, sequential screening has better test performance than cell-free DNA.[4]

NIPT provides a good opportunity to change prenatal genetic testing, but the process must be closely monitored by the scientific community. Before cell-free DNA is adopted for primary population screening further clarification is needed, including whether this test is truly needed or whether we are creating artificial market needs, whether NIPT should be the standard screening test for all pregnant women, and "what to test for?"

The scientific community should exercise careful control and not be overwhelmed by the progress.

Fortunato Lonardo head
fortunato.lonardo@ao-rummo.it
Scarano Gioacchino coordinator, Medical Cytogenetics and Molecular Genetics Unit, AORN "Gaetano Rummo," 82100 Benevento, Italy

1 Chitty LS, Kroese M. Realising the promise of non-invasive prenatal testing. *BMJ* 2015;350:h1792. (10 April.)

Cite this as: *BMJ* 2015;350:h2518

RUGBY INJURY SURVEILLANCE

EuroTag rugby league: a semi-contact version of the game

I agree that governments should not promote the full tackle form of rugby in schools.[1] We at Rugby League Ireland have developed a semi-contact version of the game, which can be used as a broad participation version and a pathway for those who want to play the full game after school. With that in mind, we have codified a set of rules that reduces the chances of collision injuries and develops the rugby skills that an overemphasis on collisions often neglects. We have called it EuroTag rugby league (it has a Facebook page with videos of the game in action and a link to the rules).

Touch rugby is often dismissed as being too soft, but EuroTag, with its limited contact, might appease people who criticise Freitag and colleagues' stance. EuroTag takes away the physical advantage that early developers have and allows some level of contact (a bit higher than basketball). Even though full tackles are not allowed, getting a "tag" on the ball requires defenders to get their feet closer to the ball carrier than in conventional touch and tag, so our version is better preparation for tackling for those who wish to continue playing the game. The game also encourages the development of ball handling and evasion skills. Players would still benefit from the camaraderie and lessons that winning and losing as a team can bring, but with a massively reduced injury risk compared with rugby union and league.

Desmond J Foy leisure centre manager, Rugby League Ireland, Dublin 2, Republic of Ireland
desmond_foy@hotmail.com

1 Freitag A, Kirkwood G, Pollock AM. Rugby injury surveillance and prevention programmes: are they effective? *BMJ* 2015;350:h1587. (21 April.)

Cite this as: *BMJ* 2015;350:h2504