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Invited Commentary

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Depression is both psychosocial and biological; antidepressants are both effective and in need of improvement; psychiatrists are both caring human beings and doctors who prescribe medications. Can we all agree on this? a commentary on 'Read & Moncrieff – depression: why drugs and electricity are not the answer'

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When I submitted my (signed) referees' comments for the editorial on antidepressant and ECT by Read and Moncrieff (2022) recently published in Psychological Medicine, I had hoped that there was an opportunity for the authors to incorporate, or at least acknowledge, my comments (and those of fellow referees) into a piece that was less divisive, and more nuanced, than usual.

A piece that was open to acknowledge the limitations on both sides of the debate, that would try to convey the complexity of these topics, and that would express some respect for the many psychiatrists and psychologists, clinicians and scientists, that try to improve the burden of depression through research on the brain, or through a clinical activity that uses all the tools available to clinicians: medications, ECT, psychotherapy, social prescribing, lifestyle changes.

A piece that would have helped patients understand what we know, and what we don't know, about why antidepressants are helpful for some of them (but not all), and have side effects that can be challenging for some of them (but not all).

Alas, the authors have sticked to the usual script of 'storming in, guns blazing'. Perpetuating a 'culture war' within mental health sciences that is damaging our community, and the community of patients. What a missed opportunity.

So, I have done what I had suggested them to do. I have written a piece that tries to put together their point of view with the available evidence, while acknowledging the complexity of the debate.

Depression is *both* 'a condition that causes abnormal feelings and behaviours', and 'a physical condition'

What else can depression be, if not 'physical'? Emotions and behaviours are physical – they have a biological substrate in the brain and in brain cells (even if we do not yet fully understand this biological substrate).

The only alternative to this view is that the mind is an independent, non-physical entity: that it is, basically, a 'spirit', a 'soul' (Pariante, 2016). Do the authors believe that abnormal emotions and behaviour reside within some non-physical entity, unrelated to the brain? If not, it must be physical. They should acknowledge this.

Why is it so difficult to say – yes, the brain regulates emotions and behaviours, in the same way that the heart pumps blood, the stomach absorbs nutrients, and the spleen hosts immune cells?

Hippocrates said it: *Men ought to know that from the brain and from the brain only arise our pleasures, joys, laughter and jests as well as our sorrows, pains, grieves and tears.*

Depression is *both* 'a kind of medical illness caused by various forms of biological deficits' and 'an emotional response to unwanted circumstances that requires human support and understanding'

Aren't we supportive and understanding to all people who are struggling with cancer, diabetes, dementia, rheumatoid arthritis, COVID? Yet we acknowledge the biological deficits associated with their conditions, and help these patients with medications – and with rehabilitation, psychosocial support and lifestyle interventions, as we do in depression.

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Yes, depression is an emotional response to unwanted circumstances, *and* yes it can be helped by medications. These two statements are complementary, not mutually exclusive.

Yes, 'antidepressants do not tackle the causes of depression' – but most of the other medications that we use in medicine also do not tackle the causes of the disorder

Painkillers take the pain away, not the cause of the pain; anti-hypertensives lower blood pressure, they do not cure hypertension; statins lower cholesterol, they do not cure the genetic problem that generates the high levels. Dexamethasone and heparin save people infected by COVID, even if these drugs do not even remotely affect the virus infection. And so on, and so forth.

Arguably, only antibiotics or antivirals tackle the cause of a disorder. Or surgery (and not every time).

Why should medications for depression have a different *value threshold*? Why should antidepressants only be relevant if they act on the cause of the disorder?

And yes, antidepressants work 'through the modifications of normal brain function', and most medications in medicine work through the modifications of *normal bodily functions*: sympathetic activity, kidney function, coagulation, immunity, gastric secretion, pain receptors: these are all *normal bodily functions*.

Yes, there is 'a small difference' between antidepressants and placebo using multi-items depression rating scales – but antidepressants specifically, robustly and consistently improve depressed mood

The Hamilton Depression Rating Scale, still widely used in clinical trials because it is indicated by regulatory agencies, was published before I was born (believe me, that was a long time ago) (Hamilton, 1960), at a time when the only antidepressants available were tricyclics and (old) MAO inhibitors. The effects of these antidepressants on some of the individual items of the scale (which include many physical symptoms, like sleep, energy, appetite and libido) were different from those induced by the more recent, widely used selective serotonin reuptake inhibitors. Because of this, there is evidence that the total score of this multi-item scale underestimates the efficacy of the newer antidepressants (Hieronymus, Jauhar, Østergaard, & Young, 2020).

The key question is: *are antidepressants, in fact, anti-depressant?*

Yes, they are, because they specifically, robustly and consistently improve depressed mood (Hieronymus, Emilsson, Nilsson, & Eriksson, 2016, Lisinski, Nilsson, & Eriksson, 2018). The 'number needed to treat' (NNT) for antidepressants, a clinically-relevant measure of the effectiveness of medications, is around 7–10, which is similar to medications for other disorders (Leucht, Hierl, Kissling, Dold, & Davis, 2012).

Are antidepressants perfect drugs? The best we can ask for? Of course not.

Even with multiple medication exposures, one-third of individuals do not achieve full symptomatic remission, and even fewer meet the criteria for both symptomatic and functional remission (Sforzini et al., 2021). Side effects, including withdrawal effects at suspension, can be challenging for some patients, as recent guidelines from the Royal College of Psychiatrists (2019) emphasise.

We need to conduct more research and get better medications.

The most recent appraisal of evidence on ECT confirms that ECT results in decreased risk of suicide, improved functional outcomes and quality of life, and decreased rates of rehospitalization

I am citing from the most recent review on this topic, published only a few days ago in the New England Journal of Medicine (Espinoza & Kellner, 2022).

It goes on by saying: 'Trials of ECT for major depressive disorder in patients with treatment-resistant depression have shown pooled response rates of 60% to 80% and pooled remission rates of 50% to 60%'.

It finishes by saying: 'Stigma and lack of access to treatment have contributed to the underuse of ECT.'

There is humongous evidence that there are 'neurochemical abnormalities in people with depression'

Changes in the size of brain areas. Change in how brain areas communicate with each other. Changes in brain cells examined in post-mortem tissue. Changes in the components of the cerebrospinal fluid. Changes in blood components that affect the brain. Changes in components of the saliva, urine, and microbiome – that also affect the brain. A myriad of replicated findings (Otte et al., 2016).

A search for 'brain and depression human studies' in PubMed just brought up around 50 thousand papers. They cannot all be wrong, and they cannot all be ignored.

Antidepressants are one of the tools to help patients coping with the 'life circumstances' and the 'social conditions' that causes these 'emotional reactions', while we are waiting (and hoping) for society to change

Imagine that you are a patient with cancer, and that you are told that the reason why you have cancer is a combination of genetic predisposition and of societal factors that are worsened by adverse life circumstances, such as lack of healthy food and high pollution levels in the area where you live now or grew up as a child. This is an accurate statement, and it would be equally accurate for a patient with depression, although we would need to add poverty, discrimination and abuse as additional societal factors.

Now imagine saying to this patient with cancer that, since the causes of cancer are societal, they should not be receiving any pharmacological treatment, but instead all the efforts should be focussed on improving society.

And, of course, that they should not trust materialistic oncologists that just want to give them chemotherapy, which does not tackle the societal causes of their cancer.

What would people with cancer say? What would *people* say?

Yet, this is what this Editorial is suggesting we say to people with depression. To people who might not be able to go to work, to have a supportive family life, or to experience pleasure in every-day activities. People who might be considering, or planning, to take their own lives. People who might be tired, sleepless, unable to eat and drink.

Surely this cannot be what the authors truly mean?

I agree with the authors when they say that we all need 'a dependable income, housing, secure and rewarding employment, engaging social activities, and opportunities to form close relationships.' I sincerely do. I have used my voice to advocate for pregnant women, children with no food, and youth involved in the 2012 riots (Pariante, 2019, 2020, 2021).

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But – what do we do to help patients with depression, while we are fighting for societal changes?

Yes, people with depression 'need to be cared for, reassured with kindness and hope, reminded of times when they have felt good'. Yes, they can be helped by exercise, psychotherapy and social prescribing.

And yes, when clinically indicated, they will need, and benefit from, antidepressants.

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