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Rational antidepressant use

In her contribution to the 'Against the Stream' series, Dr Moncrieff[1] articulates the case for the drug-centred model of antidepressant action. She notes that antidepressants do not typically outperform placebo in well-designed studies (particularly in rare instances where an active placebo is used as a control[2]), have little clinical effect and can cause serious adverse effects. Having made the case that antidepressants are not 'specific' antidepressant agents, she makes some comments about their use in clinical practice. I would like to offer a few remarks about these issues, including some musings about what 'rational antidepressant use' might look like.

Modern psychiatric practice has seen the rise and fall of several promising antidepressant agents (the monoamine oxidase inhibitors, the tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs)). Recent efforts include testing the possible antidepressant properties of ketamine. But are these efforts futile? Perhaps yes, perhaps no. A truly specific antidepressant drug (if one is ontologically possible) appears to be a pipedream, given current diagnostic limitations. Our categorisation of major depressive disorder is highly heterogeneous,[3] creating a disjunctive category of cognitive, behavioural and biological symptoms that do not reliably cluster together. Even if any of our current drugs had specificity for 'depression', this would be extremely difficult to uncover in clinical practice or research settings. As a result, drug development will be prone to ideological, as opposed to scientific, revolutions.[4]

Should we therefore abandon antidepressants as a treatment modality? As long as we are honest with our patients about our current state of knowledge, I think not. Drug use has always been an integral part of human life,[5] helping to alleviate life's various physical, emotional and existential pains. Antidepressants are no different in this respect. While researchers continue the search for a discrete condition called 'depression', drugs such as the SSRIs can be exploited for particular patient complaints. Antidepressants can cause emotional blunting, sedation, activation and decreased libido, among other things. Some have a proclivity towards one effect more than others. These effects can be exploited to relieve particular problems (e.g. sedation to alleviate insomnia, or emotional numbing to transcend an episode of intense anxiety or distress), without pretence towards a yet-to-be discovered condition. A rational provider would match a drug's effects to the patient's complaints, irrespective of diagnosis (or drug class); and would remain vigilant to the development of any adverse effects or deterioration of condition, start at the lowest recommended dose, and withdraw the patient from the drug as soon as possible. Psychosocial interventions can remain an important part of treatment, in many cases being the first treatment of choice. Antidepressants, like all drugs, are neither angels nor demons. They should be used selectively and thoughtfully, when used at all.

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Author's reply: In response to Dr Jauhar and Professor Young, I am used to being accused of using ideology, of being selective, of not being balanced or of being polemical. I take no personal offence, but it is important to point out that this is a useful tactic if you want to shut down debate. It harnesses the authority of science to present one view as neutral, objective and credible, and the other as self-interested and unreliable. In truth, we all bring assumptions and biases to our work. I am obviously unable to describe every study ever done on antidepressants in a short article, but I have written books and papers that address all the evidence I could find that supports the disease-centred model of drug action in relation to antidepressants and other psychiatric drugs.[1]

Indeed, one of the most important points I am making in relation to drug action is that existing psychopharmacological research is based on unexamined assumptions about how drugs work. These consist of the idea that drugs target the neurological mechanisms underlying symptoms, whether the latest theory about mechanisms concerns abnormalities of neurotransmitters, neural networks or neuro-plasticity. This idea has allowed psychopharmacology research to ignore the alterations to normal functioning that psychiatric drugs produce, and that will affect mental states including mental disorders, regardless of the underlying mechanisms.

Jauhar and Young point out that the latest meta-analysis of antidepressant trials finds impressive odds ratios for effects of antidepressants, but it analyses categorical outcomes derived

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from continuous data, which has been shown to inflate drug–placebo differences.[2] Network analysis is also likely to exaggerate differences, since the degree of improvement in comparative trials is higher than in placebo-controlled trials.[3] The continuous data, which showed a standardised mean difference (SMD) of 0.3, is in line with other meta-analyses in showing small and almost certainly clinically insignificant differences between antidepressants and placebo, equivalent to around two points difference on the Hamilton Rating Scale for Depression (HRSD).[4,5]

Jauhar and Young make a good point about the validity of the HRSD, but it is nevertheless used as the primary outcome of most trials. Analyses of the subjective mood item are thus more likely to be influenced by selective reporting of positive findings. However, they are wrong about the Medical Research Council trial, where the dose of imipramine was 200 mg and that of phenelzine was 60 mg. There is indeed evidence either way on the association between severity and antidepressant response, but even in studies with positive findings, effect sizes in those with severe depression are small and unlikely to be clinically significant, and the association may be accounted for by differing expectations in people with more or less severe symptoms.[6]

I agree with the gist of Dr Dunleavy's response. Recommending antidepressants because they produce emotion-blunting effects, or other useful mental alterations (sedation with tricyclics, for example), is a drug-centred model of prescribing. I don't have a problem with this as long as the patient is properly informed that placebo-controlled trials suggest little if any superiority of antidepressants, that they have full knowledge of all the potential adverse effects, and that they are quite clear that the idea that antidepressants correct an underlying chemical imbalance is not supported by evidence. Then they can make their own informed decision.

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Unlocking an acute psychiatric ward: open doors, absent patients?

In their recent paper, Beaglehole and colleagues[1] reported on the effects of unlocking an acute psychiatric ward. Despite a 58% increase in unauthorised absences and an 8% increase in violent incidents, they concluded that a less restrictive environment had some positive effects, most notably a reduction in the total hours of seclusion per month.

Our service has recently undertaken a similar transition from a locked acute ward opened (and locked) in the 1930s, to an unlocked newly built unit opened in 2016. When comparing the 6 months before and after this transition, we too found that the rate of unauthorised absences increased by 100% from a mean of 4 to 8 per month. Unlike Beaglehole, however, we observed a decrease in rates of violent incidents by 27.4% (from a mean of 31.7 to 23 per month), and an increase in the total hours of seclusion per month by 213.4% (from a mean of 28.21 to 88.42 hours per month). Of note, admission rates increased from a mean of 20 to 23 per month during the same time period.

Although a reduction in the rate of violent incidents (and, in the case of Beaglehole, reduced levels of seclusion) strengthens the case for provision of care in unlocked settings, should we be concerned about the increased rate of unauthorised absences found in both studies?

The largest available study on this topic[2] would suggest not. In their 15-year observational study involving 145,738 German in-patients, Huber *et al* concluded that locked doors do not prevent suicides, or indeed unauthorised absences.

Although a rare event, suicide is undoubtedly one the most feared outcomes when any patient absconds. Preventing harm to self or others is often the main rationale for in-patient admission. It is also a ubiquitous criterion for involuntary admission. Consequently, preventing harm is one of the main motives for locking psychiatric units.

In our study, 86% of unauthorised absences over the 1-year study period were by involuntarily admitted patients. In opening our doors, are we doing these individuals a disservice by giving them the opportunity to leave hospital at a time when they are most unwell?

Previous studies have reported on the negative consequences of absconding for patients (interrupted treatment, suicide), staff (anxiety), family members (loss of trust in the service), and emergency services (expended resources).[3] It could be argued that a reduction in the number of violent incidents (and, in Beaglehole's case, seclusion) is worth the risk of these adverse outcomes. In our view, however, a modern purpose-built environment coupled with increased staffing levels better explains these findings. Increased numbers of nursing staff result in improved relational security, an important element of therapeutic security provided by higher staff-to-patient ratios.[4]

Our study and that of Beaglehole and colleagues indicate that unlocking acute psychiatric wards leads to an upsurge in unauthorised absences. The majority of patients who absconded were admitted involuntarily. We suggest that acute mental health services give careful consideration to all the risks associated with unauthorised absences before opening their

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